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Case Series

Internal Medicine Section

Atypical Presentation of Acute Myeloid Leukaemia: A Series of Three Cases

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ABSTRACT

Acute Myeloid Leukaemia (AML) is a haematological malignancy characterised by the infiltration of the blood, bone marrow and other tissues by proliferative, clonal, poorly differentiated cells of the haematopoietic system. Diagnosis can be suspected by the presence of atypical cells on a peripheral blood smear and confirmed by bone marrow aspiration studies and immunohistochemistry. Detection of AML in the first trimester of pregnancy is a rare phenomenon. The rarity of haematological malignancies, especially in the first trimester, poses challenges in the diagnosis, treatment and management of leukaemias during pregnancy. AML masquerading as acute and chronic infections also presents diagnostic and consequent therapeutic challenges. Hence, multidisciplinary treatment is key to the outcomes of these rare presentations. The following is a case series highlighting the varied ways in which AML can present to a physician, often requiring a high degree of suspicion to warrant further investigation. The first case discusses the difficulties encountered in diagnosing and treating a primigravida woman in her first trimester, which ultimately led to the termination of her pregnancy and subsequent chemotherapy cycles. The second case involves a female in her 40's presenting with complaints of chronic sinusitis, who was diagnosed with AML upon evaluation. This case was challenging as infiltrative lesions of leukaemia were considered during the assessment. The patient was managed with a carefully formulated regimen of chemotherapeutic agents and antibiotics. The third case presented with acute pyelonephritis, illuminating the rapid deterioration associated with the perils of undiagnosed haematological malignancies. Together, these three cases underscore the various presentations of AML, highlighting the necessity for a high degree of suspicion even in seemingly uncomplicated cases such as chronic sinusitis or acute abdominal pain, such as pyelonephritis. Haematological malignancies are commonly suspected when more aggressive symptoms, such as fever, bleeding gums, or generalised lymphadenopathy, are present. This case series aims to draw attention to the simpler presentations that may be overlooked in outpatient settings as benign infections.

Keywords: Oncology, Pregnancy, Pyelonephritis, Sinusitis

INTRODUCTION

An acute form of myeloid leukaemia, known as AML, has the potential to invade almost every organ system. AML is characterised by a clonal proliferation of the myeloid series in the marrow, leading to the aggressive presentation of the haematological picture, with immature blast cells. The phenotypes of this disease are varied, presenting widely with symptoms such as fever, bleeding gums and lymphadenopathy. In certain cases, the management of AML can pose significant challenges due to concurrent infections, blast crisis, co-morbidities and, in some instances, even pregnancy and lactation [1]. The management of AML during pregnancy, in particular, presents a notable clinical challenge. Furthermore, the presentation of AML masquerading as both acute and chronic infections can create diagnostic and therapeutic challenges that do not allow much time for resolution. This report summarises a series of three cases with extremely uncommon presentations of AML, aimed at improving the understanding and management of what can prove to be an aggressive disease. This article strives to underscore the importance of the sharp clinical acumen required to diagnose these unusual presentations of AML.

CASE SERIES

Case 1

A 23-year-old female patient, who was 15 weeks into her gestation, presented with a history of nausea, vomiting and loose stools for the past 5-6 days. The patient reported multiple episodes of vomiting per day in the week leading up to her presentation to the hospital. The vomiting episodes were non projectile, non bilious, contained food particles and were not associated with blood. This was accompanied by several episodes of loose stools, which were mucoid in consistency, black in colour and tarry in appearance. She experienced associated abdominal pain that was dull, aching and diffuse in character, present throughout the day and occasionally relieved by defecation. There was no associated per vaginal leakage or bleeding. The patient did not report any history of fever, yellowish discolouration of the eyes, burning micturition, or blood in the urine. At this point, a differential diagnosis of acute gastroenteritis, hepatitis, cholecystitis and even hyperemesis gravidarum was considered.

Upon further evaluation for causes of fever, the patient was incidentally found to have pancytopenia. Laboratory values from three months prior to conception were normal [Table/Fig-1]. The initial laboratory parameters of the patient upon presentation, including a negative fever panel, are tabulated in [Table/Fig-2].

Blood investigations prior to conception	Patient values	Reference range
Haemoglobin (gm/dL)	13.60	11.6-15.0
Total leukocyte count (/µL)	9900	4000-100000
Platelets (/µL)	334000	150000-410000

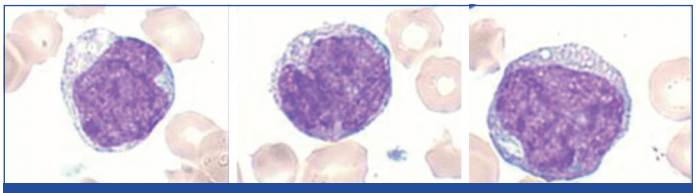
[Table/Fig-1]: Laboratory investigations 4 months prior to presentation.

Over the next few days, the patient was managed symptomatically for her gastroenteritis complaints. She was started on broad-spectrum antibiotics, such as Inj. Ceftriaxone 1 gm intravenously twice a day and Inj. Metronidazole 500 mg intravenously three times a day for the next five days. She was given antiemetic measures and antidiarrhoeal agents to control her symptoms. An ultrasound of the abdomen and pelvis suggested grade II liver fibrosis, with no other obvious anomalies. There was no evidence of splenomegaly, both clinically

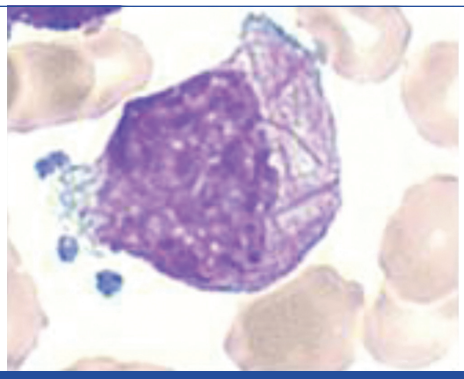
Initial blood investigations	Patient values	Reference range
Haemoglobin (gm/dL)	8.80	11.6-15.0
Total leukocyte count (/µL)	800	4000-100000
Platelets (/µL)	20000	150000-410000
Total bilirubin (mg/dL)	0.71	Up to 1.2
Direct bilirubin (mg/dL)	0.31	Up to 0.5
Serum Glutamic Oxaloacetic Transaminase (SGOT) (U/L)	20	8-48
Serum Glutamic Pyruvic Transaminase (SGPT) (U/L)	16	7-55
Serum proteins (g/dL)	6.90	6.4 to 8.3
Albumin (g/dL)	4.10	3.5 to 5.2
Creatinine (mg/dL)	0.82	0.6 to 1.2
Urea (mg/dL)	18	17 to 49
Prothrombin time (secs)	12.60	10.35-12.90
INR value	1.06	0.85-1.15
Dengue	Negative	-
Widal	Negative	-
Rapid malaria test	Negative	-
HbA1C (%)	5.5	4.0-5.6
Sodium (mmol/L)	139	136-145
Potassium (mmol/L)	3.53	3.50-5.10
T3 (ng/mL)	1.81	0.64-1.52
T4 (µg/mL)	11.2	4.87-11.72
TSH (µIU/mL)	0.61	0.1-2.5 (First Trimester)

[Table/Fig-2]: Laboratory investigations on day of presentation (Case 1).

and radiologically. The antenatal scan demonstrated monochorionic monoamniotic gestation with a single live intrauterine foetus at 14 weeks of gestation. No obvious foetal anomalies were noted. Following this, she underwent a bone marrow aspiration and biopsy, which revealed the replacement of the bone marrow haematopoietic material by 60% blast cells. The blast cells had an increased N:C ratio, with a few cells showing Auer rods [Table/Fig-3]. Faggot cells, showing numerous Auer rods in the cytoplasm, were also visualised [Table/Fig-4]. This picture was suggestive of AML. On flow cytometry, the morphological and immunophenotyping findings were suggestive of Acute Promyelocytic Leukaemia (APML). Further cytometric analysis by fluorescence in situ hybridisation was positive for the PML::RARA fusion, which is diagnostic of APML [Table/Fig-5-7].



[Table/Fig-3]: Abnormal promyelocytes which are intermediate in size have moderate nuclear: cytoplasmic ratio, fine chromatin and scanty to moderate cytoplasm.



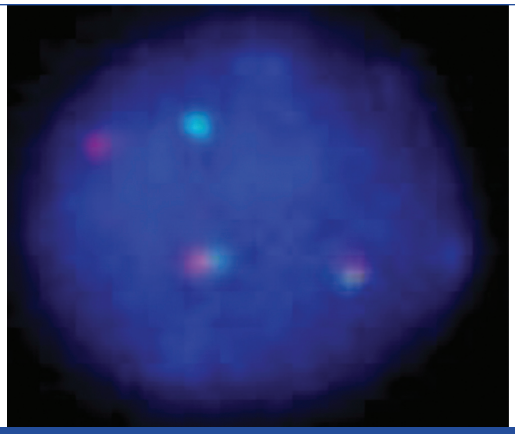
[Table/Fig-4]: Faggot cells, seen in hyper granular forms of acute myeloid leukaemia, showing numerous Auer rods clumped together giving the appearance of a bundle of sticks.

Probes used	Results	International System for Human Cytogenomic Nomenclature (ISCN) nomenclature (2020)
PML::RARA dual Colour dual fusion Probe	Abnormal	Nuc ish (PML, RARA)×3 (PML con RARA×2) (95/170)

[Table/Fig-5]: Result of fish test for PML::Rara fusion gene.

Number of cells analysed	Interpretation	Result
170	56% cells Positive for PML::RARA fusion	Abnormal

[Table/Fig-6]: Fish Test indicating Green- 17q21 (RARA gene), Orange- 15q24 (PML gene).



[Table/Fig-7]: Probes used for fish test for PML::Rara fusion gene.

The patient had just entered her second trimester of pregnancy. A multidisciplinary approach was considered and in consultation with the obstetric and oncology teams, the following treatment options were presented to the patient: institution of chemotherapy after termination of pregnancy, continuation of pregnancy with chemotherapy and the possibility of in-vitro fertilisation postchemotherapy for future pregnancies. In this case, the patient was initiated on chemotherapy following a medical termination of pregnancy. Remission was induced with all-trans retinoic acid. The patient is currently stable and continuing chemotherapy at present.

Case 2

A 43-year-old female presented to the hospital with complaints of obstructive nasal symptoms on and off for four months. The patient reported experiencing low-grade fever intermittently and headaches, predominantly in the frontal regions bilaterally, which were throbbing in nature and had worsened over the past five days. She had not undergone any surgeries in the past.

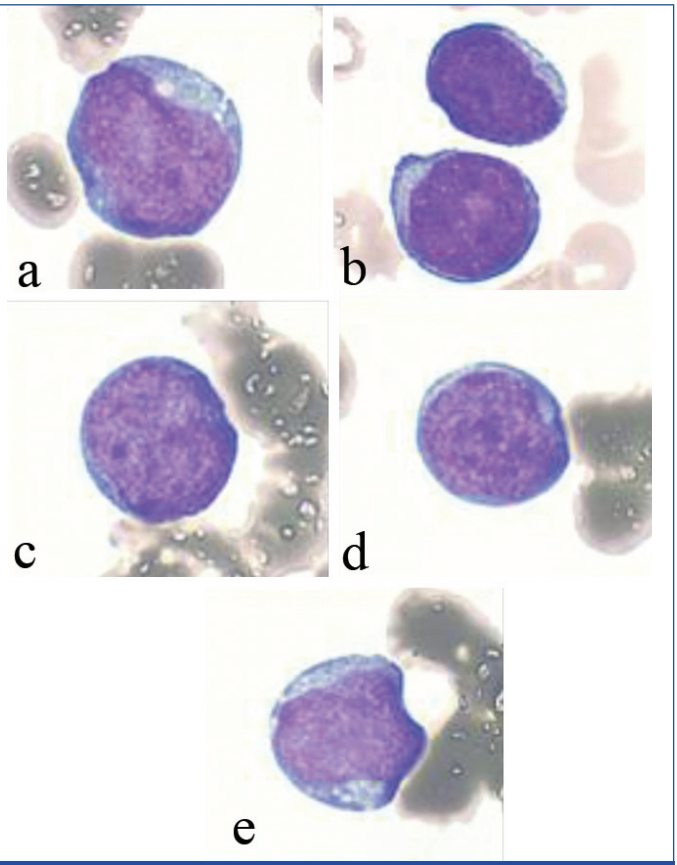
On evaluation, she was pale, afebrile and vitally stable. Further laboratory examination revealed a haemogram showing a pancytopenic picture, with no other obvious laboratory derangements, the details of which are summarised in [Table/Fig-8].

Initial blood investigations	Patient values	Reference range
Haemoglobin (gm/dL)	8.40	11.6-15.0
Total leukocyte count (µ/L)	1500	4000-100000
Platelets (µ/L)	33000	150000-410000
Total bilirubin (mg/dL)	1.31	Upto 1.2
Direct bilirubin (mg/dL)	0.73	Upto 0.5
SGOT (U/L)	15	8-48
SGPT (U/L)	35	7-55
Serum proteins (gm/dL)	6.70	6.4 to 8.3
Albumin (gm/dL)	4.00	3.5 to 5.2
Creatinine (mg/dL)	0.68	0.6 to 1.2
Urea (mg/dL)	17	17 to 49
Dengue	Negative	-

Widal	Negative	-
Rapid malaria test	Negative	-
HbA1C (%)	5.8	4.0-5.6
Sodium (mmol/L)	132	136-145
Potassium (mmol/L)	3.83	3.50-5.10
T3 (ng/dL)	0.59	0.64-1.52
T4 (µg/dL)	7.54	4.87-11.72
TSH (µlU/mL)	1.05	0.35-4.94

[Table/Fig-8]: Laboratory investigations on day of presentation (Case 2).

Consequently, a bone marrow aspiration and biopsy were planned. The biopsy report revealed the presence of 12% atypical cells, medium to large in size, with an increased nuclear: cytoplasmic ratio, hyperchromatic nuclei, occasional nucleoli and a moderate amount of cytoplasm, signifying myeloid cell proliferation and AML [Table/Fig-9].



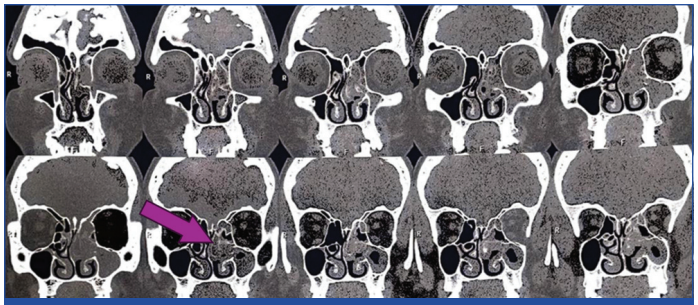
[Table/Fig-9]: Atypical cells found in patient's bone marrow aspirate. a-e) All depict atypical blast cells with increased nuclear: cytoplasmic ratio, hyperchromatic nuclei and scant to moderate cytoplasm.

Simultaneously, a CT paranasal sinus was planned. Computed tomography of paranasal sinuses depicting polypoidal mucosal thickening of left maxillary sinus with erosion of medial wall of maxillary sinus, ostium, superior and middle meatus [Table/Fig-10,11]. These findings were suggestive of chronic maxillary sinusitis.

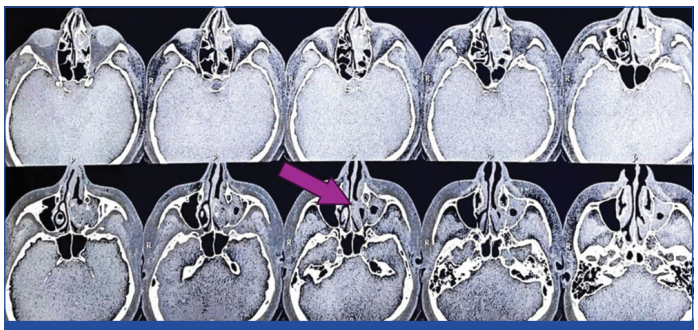
The patient consequently underwent functional endoscopic sinus surgery and was initiated on chemotherapy two weeks after the success of the procedure. On follow-up, she was doing well on treatment, with a few gastric issues managed with proton pump inhibitors. She had no complaints of fever, only persistent weakness and was compliant with her chemotherapy schedule.

Case 3

A 47-year-old female, known to be hypertensive for the past five years, presented to the outpatient department with complaints of right-sided flank pain, fever and weight loss for one month. The patient was experiencing right-sided dull aching pain, with no specific aggravating or relieving factors. She complained of intermittent fever over the past month. On evaluation, she had pancytopenia [Table/Fig-12].



[Table/Fig-10]: Coronal section of computed tomography of paranasal sinuses depicting polypoidal mucosal thickening of left maxillary sinus with erosion of medial wall of maxillary sinus, ostium, superior and middle meatus (marked by purple arrow).

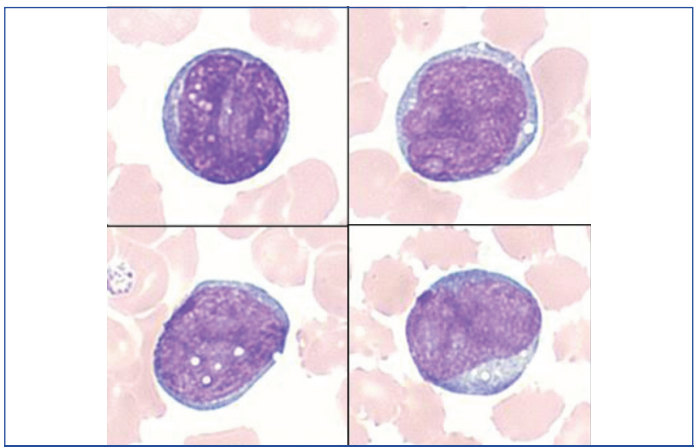


[Table/Fig-11]: Axial section of computed tomography of paranasal sinuses depicting polypoidal mucosal thickening of left maxillary sinus with erosion of medial wall of maxillary sinus, ostium, superior and middle meatus (marked by purple) arrow).

Initial blood investigations	Patient values	Reference range
Haemoglobin (gm/dL)	6.40	11.6-15.0
Total leukocyte count (µ/L)	800	4000-100000
Platelets (µ/L)	14000	150000-410000
Total bilirubin (mg/dL)	0.99	Upto 1.2
Direct bilirubin (mg/dL)	0.45	Upto 0.5
SGOT (U/L)	20	8-48
SGPT (U/L)	27	7-55
Serum proteins (g/dL)	6.10	6.4 to 8.3
Albumin (g/dL)	4.10	3.5 to 5.2
Creatinine (mg/dL)	1.02	0.6 to 1.2
Urea (mg/dL)	47	17 to 49
Dengue	Negative	-
Widal	Negative	-
Rapid malaria test	Negative	-

[Table/Fig-12]: Initial blood investigations on day 1.

She experienced continuous fever spikes during her hospital stay. A bone marrow aspiration and biopsy were performed to evaluate the pancytopenia and the smear showed atypical cells, as detailed in [Table/Fig-13].



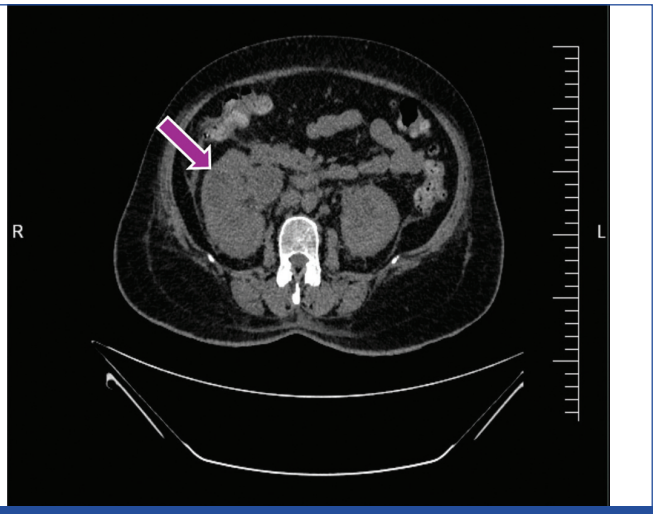
[Table/Fig-13]: Smear showing increase in blasts, intermediate to large in size, with high nuclear: cytoplasmic ratio, fine chromatin, 0-1 nucleoli and scant cytoplasm.

A diagnosis of AML was made and upon flow cytometric analysis, the majority of mononuclear cells were positive for CD13, CD34, CD38, CD123 and CD117, denoting the phenotype of the cells [Table/Fig-14].

Antibody	Expression	Percentage
CD22	Negative	
CD19	Negative	
CD10	Negative	
CD34	Dim-mod	97.6%
CD71	Negative	
CD20	Negative	
CD7	Negative	
CD3	Negative	
CD4	Negative	
CD8	Negative	
CD13	Moderate	94.0%
CD16	Negative	
CD15	Negative	
CD33	Heterogenous	69.6%
HLADR	Dim-mod	96.7%
CD64	Negative	
CD14	Negative	
CD38	Moderate	98.5%
AntiMPO	Negative	
cCD79a	Negative	
cCD3	Negative	
TdT	Negative	
CD123	Dim	95.7%
CD117	Moderate	97.0%
CD11b	Negative	

[Table/Fig-14]: Flow cytometric analysis showing positivity for CD 13,34,38,123,117.

A computed tomography scan of the abdomen and pelvis revealed right-sided changes suggestive of emphysematous pyelonephritis [Table/Fig-15]. The patient was immediately initiated on Injection Meropenem 500 mg twice daily. After four days of strict monitoring, chemotherapy was initiated for AML.



[Table/Fig-15]: Computed tomography of the abdomen and pelvis showing a bulky kidney with air foci within the medulla. This was consistent with the findings of right-sided emphysematous pyelonephritis (depicted by purple arrow).

The patient experienced continuous fever spikes, which were controlled with intravenous antipyretics. She was initiated on anti-hyperuricaemic therapy and hydration prior to an escalated chemotherapy regimen with venetoclax and cytarabine. The patient completed six cycles of treatment and is currently following-up.

DISCUSSION

The AML is a type of aggressive cancer that originates in the bone marrow, the tissue responsible for producing blood cells [2]. It occurs when there is a clonal expansion of abnormal haematopoietic precursor cells, particularly from the myeloid lineage, leading to the rapid growth of immature cells, or "blasts," that fail to develop into healthy blood cells. These leukaemic cells accumulate in the bone marrow and bloodstream, impeding the production of normal red blood cells, white blood cells and platelets. This disruption can cause symptoms such as anaemia, increased susceptibility to infections, easy bruising or bleeding and fatigue. AML is characterised by its fast progression and requires prompt diagnosis and treatment, typically involving chemotherapy, targeted therapy and sometimes bone marrow or stem cell transplantation [3].

Leukaemia in a pregnant patient can have severe consequences for both the mother and the foetus. AML is associated with complications such as leukocytosis, thrombosis and coagulopathy, all of which substantially increase maternal mortality [4]. Beyond maternal complications, leukaemia during pregnancy also poses considerable risks to the foetus. These include an increased likelihood of spontaneous abortion, intrauterine growth restriction and perinatal mortality. The pancytopenic state associated with AML heightens the risk of infections, while potential placental ischaemia further compromises foetal wellbeing [5]. The treatment of AML, particularly during early pregnancy, presents additional concerns. The administration of chemotherapy during the first trimester carries the highest risk, often leading to miscarriage, foetal death and congenital malformations [6,7]. Therefore, careful consideration must be given to balancing maternal treatment efficacy with foetal safety in the management of AML during pregnancy [7].

In the second case, the patient was incidentally detected with pancytopenia during evaluation for unilateral nasal obstruction. An invasive form of maxillary sinusitis was identified upon evaluation. Sinusitis in AML has, in previous reports, been associated with myeloid sarcoma [8], which is the invasion of the soft-tissue of the paranasal sinuses by malignant blast cells. In this patient, the complaints had existed for quite some time but had been dismissed as a frequently acquired common upper respiratory tract infection. It was only upon further evaluation that a diagnosis of chronic invasive maxillary sinusitis was made.

In the third case, the patient presented with complaints suggestive of a complicated upper urinary tract infection. There have been reported cases of AML masquerading as xanthogranulomatous pyelonephritis [9]. In this case, the physician must maintain a high degree of suspicion to detect a manifestation of AML as serious as emphysematous pyelonephritis. Pathologically, this may be attributed to the low level of immunity that AML can cause in the body. Addressing the infection with antibiotics and antipyretics, while simultaneously initiating chemotherapy was challenging in this case. It is advised that total leukocyte counts be reduced to less than 25,000 cells/mm^3 prior to the initiation of venetoclax; hence, pretreatment cytoreduction is required in most cases [10].

CONCLUSION(S)

The above cases strive to showcase the varied ways in which haematological malignancies can mislead a physician into complacency. A high degree of suspicion may be required to further evaluate seemingly normal patients who present with complaints of upper gastrointestinal bleeding, especially if they lack any antecedent hepatic pathology. On the other hand, infections that persist despite the use of standard antibiotics and seem to develop resistance in immunocompetent patients should raise suspicion of haematological malignancies. Acute presentations, though difficult to detect and unlikely to be related to haematological disorders, may also contribute to an overlooked and often ignored spectrum of AML presentations. Treatment options should always include

aggressive chemotherapy and its rapid initiation to give patients the best chance of recovery.

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