Acute Promyelocytic Leukemia

Data Analysis

The patient is a 51-year-old male with a history of fatigue and unexplained bruising, signs and symptoms suggestive of an urgent hematologic disorder. Laboratory testing showed a complex, but significant, pattern of abnormalities. The complete blood count showed severe thrombocytopenia (27×10^9/L), which relates directly to the patient's bleeding tendency and bruising. Neutropenia (1.5×10^9/L) was observed, and evidence of severe lymphopenia (0.3×10^9/L), suggesting a significant neoplastic process was occurring (such as bone marrow replacement by neoplastic cells). The peripheral blood smear showed circulating promyelocytes (2.1×10^9/L) and myelocytes (0.6×10^9/L), suggestive of a block in myeloid differentiation, and an increased population of non-stained cells (54.9×10^9/L), likely representing blasts that the automated analyzers did not classify.

The coagulation profile was also informative, with a prolonged PT and elevated INR (1.5), and a very low fibrinogen (1.02 g/L), supporting diagnosis of disseminated intravascular coagulation (DIC) (Boral, Williams and Boral, 2016). The normal APTT ratio (0.9) helps to exclude other causes of coagulopathy from the differential diagnosis. Other laboratory markers included mild unconjugated hyperbilirubinemia (28 μM), likely suggesting low-grade hemolysis, along with an elevated CRP (35 mg/L), and indicative of an underlying inflammatory response common in hematologic malignancies.

Examination of the peripheral blood smear demonstrated several important findings. Promyelocytes noted were hypergranular with bilobed nuclei. No mature granulocytes were seen. The automatic counting as confirmed by the smear demonstrated severely reduced platelets consistent with the severe thrombocytopenia. There were sporadic nucleated red blood cells that further supported the diagnosis of a bone marrow infiltrative process.

From these observations, several important diagnostic clues emerge. The combination of pancytopenia with circulating promyelocytes and concurrent DIC would be considered pathognomonic for acute promyelocytic leukemia (APL) (Avvisati, Ten Cate and Mandelli, 2019). The degree of thrombocytopenia correlates with bleeding risks in these patients and is a major

reason to take immediate action. The immature myeloid cells in circulation confirm this as an acute leukemic process rather than a more indolent marrow disorder. Taken together, the laboratory abnormalities provide a very strong argument for APL, but confirmatory tests - including a bone marrow examination and genetic tests - are critical in making this diagnosis. Such a pattern of abnormalities must be recognized early because APL is considered a hematologic emergency, and presenting late can be fatal because of the risk of bleeding caused by coagulopathy.

Differential Diagnosis

The patient's symptoms, including pancytopenia, immature myeloid cells in the peripheral blood, and coagulopathy, necessitate considering other hematologic disorders. Although acute promyelocytic leukemia (APL) is the most likely diagnosis, we must use a methodical approach to the differential diagnosis in order to avoid both misdiagnosis and loss of the opportunity to treat promptly (Arber *et al.*, 2017).

The first alternative differential to consider is other forms of acute myeloid leukemia (AML). Acute Myeloid Leukemia with maturation (AML-M2) could present similarly with pancytopenia and blood with blasts, except APL generally has pronounced coagulopathy (Liu and Hu, 2022). Unlike APL, the t(8;21) translocation and maturation beyond the promyelocyte stage will distinguish AML-M2. Alternatively, myelomonocytic or monocyte leukemia (M4/M5) can sometimes present similarly to APL; however, they will possess markers of monocyte differentiation and are categorized with different cytogenetic abnormalities (Bhargava, 2021). Furthermore, the variants of AML, including AML-M4/M5, will likely not show the specific hypergranular promyelocytes as seen in the blood film shown in our patient.

Myelodysplastic syndromes (MDS) (especially MDS-EB) should also be considered. Even though MDS could account for pancytopenia with dysplastic findings, the acute nature of the presentation in this patient and overwhelming proportion of promyelocytes rules against this diagnosis (Hasserjian *et al.*, 2023). Moreover, MDS very rarely led to coagulopathy to the degree noted in this patient. Finally, having minimal to no dysplastic findings in the peripheral blood also reduces the likelihood of MDS involvement.

Acute lymphoblastic leukemia (ALL) may be another consideration, particularly due to the pancytopenia and circulating blasts. However, the myeloid immunophenotype (CD13+/CD33+) of the abnormal cells and the description of the cells demonstrating promyelocytes suggest ALL is unlikely. Lymphoblasts are typically associated with scant cytoplasm and condensed chromatin without such prominent granules as in APL promyelocytes (Leitinger, Kuzich and Juneja, 2021). It is also essential to rule out some of the non-leukemic causes of pancytopenia with coagulopathy. Sepsis with disseminated intravascular coagulation (DIC) can produce some of the similar aspects of this presentation, but the absence of fever, normal procalcitonin, and presence of circulating promyelocytes does not support an infectious etiology (Iba *et al.*, 2023). Severe aplastic anemia might cause pancytopenia, but would not account for the coagulopathy or circulating immature cells. Vitamin K deficiency, or liver disease, could explain the coagulopathy, but would not create the hematologic picture presented here.

The microangiopathic hemolytic anemia including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) might demonstrate thrombocytopenia and microangiopathic changes, but would typically demonstrate schistocytes on blood film and not promyelocytes (Bommer and Bloehdorn, 2025). The absence of renal impairment and neurological symptoms does not support these diagnoses.

The combination of findings in this case - especially relevant were the promyelocytes and DIC - makes APL by far the most likely diagnosis. However, a definitive diagnosis of APL will require a bone marrow evaluation with flow cytometry, cytogenetics to detect the t(15;17), and molecular testing for the PML-RARA fusion (Klausner *et al.*, 2024). Using all three diagnostic strategies ensures accurate diagnoses, but we recognize there are circumstances, like this one, where initiating treatment with all-trans-retinoic acid (ATRA) is essential for patients with APL to minimize risk of fatal hemorrhage (Matikainen *et al.*, 1996). Therefore, waiting to base management on a diagnosis should (or can) not occur. The differential diagnosis also emphasizes the need to work with morphological, immunophenotypic, and genetic data to manage acute leukemias.

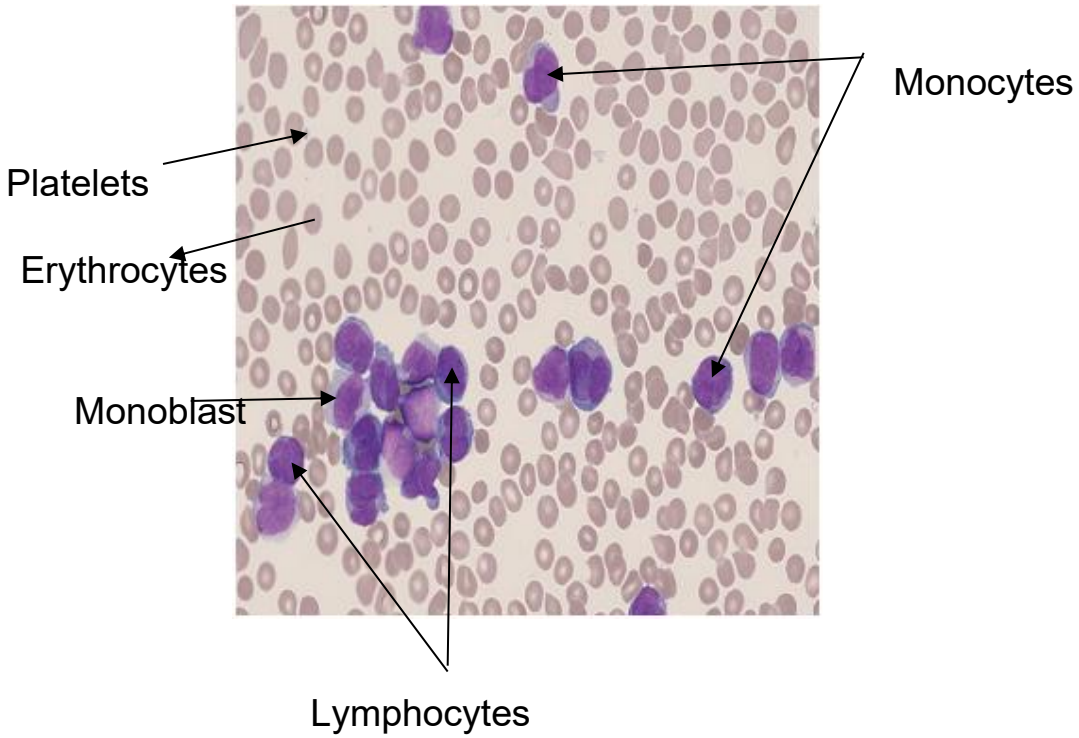

Figure: Annotated Abnormal Blood Film Photograph

Disease biology and treatment

Acute promyelocytic leukemia (APL) is a distinct version of acute myeloid leukemia with a different molecular pathogenesis. APL is the result of a reciprocal chromosomal translocation between chromosome 15 and 17 [t (15; 17) (q24; q21)] creating the PML-RARA fusion gene. Genomic translocation disrupts two important cellular processes: myeloid differentiation and apoptosis. The PML-RARA fusion transcript encodes an altered transcriptional repressor that inhibits differentiation at the promyelocyte stage of development through multiple mechanisms. First, it elicits recruitment of nuclear receptor co-repressor (N-CoR) complexes and histone deacetylases (HDACs) to retinoic acid response elements in the DNA. Second, it reconfigures the normal structure of PML bodies residing in the nucleus which is known to be involved in the tumor suppressor and apoptotic process that is irreversibly altered. Lastly, the PML-RARA fusion protein exhibits resistance to physiologic levels of retinoic acid to keep the malignant leukemic blasts in an undifferentiated state.

The coagulopathy present in APL is also thought to occur through multiple mechanisms. Malignant promyelocytes elaborate tissue factor and cancer procoagulant to initiate the coagulation cascade. They also over express annexin II on their cell surface to promote plasmin generation and hyperfibrinolysis. In summary, the combination of rising thrombin generation and hyperfibrinolysis creates a perfect storm for disseminated intravascular coagulation (DIC) which is the most life threatening complication of untreated APL.

The treatment approach for APL has changed dramatically since the advent of differentiation therapy; therapy is now individualized according to risk stratification, with the most important prognostic factor identified being white blood cell count at the time of diagnosis:

1. **Induction Therapy**

   Patients should begin ATRA as soon as APL is suspected. ATRA binds to PML-RARA, which leads to differentiation of leukemic promyelocytes through the release of co-repressors. In low/intermediate risk patients (WBC $\leq 10\times10^9$/L), ATRA is combined to arsenic trioxide (ATO) therapy—ATO reduces PML-RARA by means of SUMOylation/ubiquitination, resulting in >90% remission. ATRA, ATO and idarubicin are administered to high risk patients (WBC $>10\times10^9$/L) for rapid blast reduction and prevention of differentiation syndrome. New evidence suggests gemtuzumab ozogamicin (anti-CD33) may be beneficial to high-risk patients (Molica *et al.*, 2021). This risk-adapted approach allows for the best possible outcome with least toxicity. It is crucial to always start ATRA as soon as possible even before genetic confirmation.

2. **Consolidation Therapy**

   Once hematologic remission is achieved, the next step is to give consolidation therapy, which will consist of 2-4 cycles depending on whether the patient is low, intermediate, or high risk. For low-risk patients two cycles of ATRA plus ATO may be all that is required (Wang *et al.*, 2022). For intermediate and high-risk patients, they may still require additional cycles with chemotherapy, depending on the protocol used for induction and the patient's tolerance to therapy.

3. **Maintenance Therapy**

   At this time, the evidence suggests that low-risk patients who achieve complete molecular remission after consolidation can avoid prophylactic maintenance therapy. Conversely, high-risk patients usually receive 1 to 2 years of maintenance therapy with intermittent ATRA plus low dose chemotherapy (usually 6-mercaptopurine and methotrexate) (Ghiaur *et al.*, 2024). The role of maintenance in the ATRA/ATO era has yet to be investigated fully.

Differentiation syndrome (25-30% of patients) should be treated immediately with dexamethasone (10 mg IV every 12 hours) and discontinuation of ATRA/ATO (if severe). In case of coagulopathy, platelets should be maintained above 50×10^9/L and fibrinogen above 1.5g/L using cryoprecipitate/FFP. PML-RARA RT-PCR for molecular monitoring will occur at diagnosis, following consolidation, thereafter every quarter for 2 years and then twice yearly for 3 years (Aitken *et al.*, 2021). Most protocol derived cases are >90% cured; however, in some relapsed cases, ATO reinduction, gemtuzumab ozogamicin, or allogeneic transplant may be offered. APL is an excellent example of successful targeted therapy and research is ongoing into high-risk protocols and relapse, as well as effectiveness of supportive management, to further reduce the risk of early death with a risk-adapted approach.

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