Hematologic Emergencies in Children

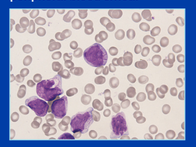
ACUTE PROMYELOCYTIC LEUKEMIA (APL)

1 WHAT IS APL? WHEN TO SUSPECT IT?

- APL is a rare aggressive subtype of acute myeloid leukemia (AML) caused by retinoic acid receptor alpha (*RARA*) gene translocations (mainly PML-*RARA*)[1]
- Cure rates are high when early death is prevented by prompt administration of ATRA (all-trans-retinoic acid) -based therapy at first suspicion of APL[1,2]
- Prominent coagulopathy is a distinguishing feature (from mild mucocutaneous hemorrhages to severe intracranial or pulmonary bleeding)[1,2]
- Patients may present with subtle signs of stroke[1]
- Early death, due to severe bleeding and thrombosis is frequent and happens days before or after presentation, usually before diagnosis is made and treatment started[1]
- APL patients with a high white blood cell (WBC) count (>10 x 10^9/L) are at much higher risk of early death from bleeding and thrombosis[1]

Bruising

Abnormal promyelocytes in peripheral blood smear

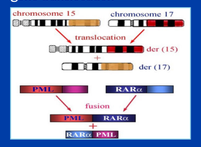


This image was originally published in ASH Image Bank. Marco Gambassi. Promyelocytes with Auer rods - 1. ASH Image Bank. 2011; #00005912. © the American Society of Hematology.

2 PROMPT DIAGNOSTIC TESTING IS CRUCIAL

- Contact a leukemia specialist immediately
- If symptoms at presentation suggest APL, the following tests should be done:
  - Peripheral blood smear and bone marrow aspirate to look for abnormal promyelocytes[2,3]
  - Blood/coagulation tests: complete blood count, international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen level, D-dimer test[2-4]
- Tumor lysis blood tests: lactate dehydrogenase (LDH), uric acid, potassium, phosphate, calcium, creatinine[4,5]
  - Genetic tests for PML *RARA* gene translocation (fluorescence *in situ* hybridization, reverse transcriptase polymerase chain reaction)

Genetic test for PML *RARA* gene translocation



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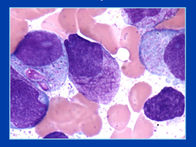
Abnormal promyelocytes in bone marrow aspirate



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3 IF CLINICAL PRESENTATION AND INITIAL TESTS ARE INDICATIVE OF APL: TREAT ON CLINICAL SUSPICION

DO NOT:

- Do not wait for genetic confirmation to begin treatment[1-3,6]
- Do not perform invasive procedures (lumbar puncture) or leukapheresis (for a high WBC count) to prevent early death from catastrophic bleeding[1,3,6]

DO:

- ✓ Contact a leukemia specialist immediately
- ✓ Start oral tretinoin (or ATRA Vesinoid®) at first suspicion of APL; consider dexamethasone for patients with presenting WBC count >10 x 10^9/L
- ✓ Immediately provide supportive care to reduce the incidence of early death from thrombo-hemorrhagic complications:[1-4,6,7]
  - Administer transfusions of:
    - Fibrinogen concentrates or cryoprecipitate (to keep fibrinogen >1.5-2 g/L)
    - Platelets (to keep counts >50 x 10^9/L or 100 x 10^9/L in case of severe intracranial or pulmonary bleeding)
    - Fresh frozen plasma (to keep INR <1.3)
  - Conduct frequent (q 4-6 hrs), ongoing clinical and laboratory monitoring of the patient
- ✓ Watch carefully for differentiation syndrome (DS): APL patients with high blood WBC counts (>5 x 10^9/L) can develop potentially fatal DS soon after treatment initiation[2,3]
- ✓ Transfer the patient to a pediatric tertiary-care centre

HYPERLEUKOCYTOSIS

1 WHAT IS HYPERLEUKOCYTOSIS?

- Life-threatening complication of pediatric leukemias (defined as a peripheral blood leukocyte count >100 x 10^9/L), such as:[7]
  - Acute lymphoblastic leukemia (ALL)
  - Acute myeloid leukemia (AML)
  - Chronic myeloid leukemia (CML)
- Medical emergency associated with early death due to hyperviscosity (caused by high leukocyte count) that can lead to cerebral and pulmonary leukostasis[7,8]
- Clinical symptoms can be neurologic, respiratory or vascular[7]
- Severe tumor lysis syndrome can develop[7,8]

2 INVESTIGATIONS

- Careful assessment for thrombocytopenia: obtain manual platelet counts (high WBC count may result in false elevation of automated platelet counts)[1]
- Careful assessment for coagulopathy (PTT, INR, fibrinogen, and D-dimer tests) and tumor lysis syndrome (LDH, uric acid, potassium, phosphate, calcium, creatinine)[5,7,8]
- Neurological exam to identify signs of cerebral leukostasis or intracranial hemorrhage; severe headaches and confusion can be early neurological signs[7,8]
- Respiratory exam to identify signs of pulmonary leukostasis: cough, crackles, hypoxia, and abnormal chest x-ray[7]

3 TREATMENT GUIDANCE

DO NOT:

- Do not transfuse red blood cells, regardless of the hemoglobin level, unless advised by a hemato-oncologist, as they can increase viscosity, leading to stroke and possibly death[7]
- Do not include potassium, calcium, and phosphate in intravenous (IV) fluids[7]

DO:

- ✓ Immediately contact a leukemia specialist
- ✓ Hydrate the patient with IV Normal Saline (NaCl 0.9%) at 2 x maintenance (**DO NOT ADD KCl**)[7]
- ✓ Transfuse platelets to correct thrombocytopenia (keep counts >40 x 10^9/L to prevent central nervous system hemorrhage)[7]
- ✓ Correct coagulopathy by giving fresh frozen plasma or cryoprecipitate in case of AML or APL[9]
- ✓ Correct hyperuricemia with IV rasburicase, hyperkalemia, and hyperphosphatemia and monitor electrolytes, uric acid, and creatinine every 4-6 hours[9]
- ✓ Consider admission to an intensive-care unit if leukapheresis is available and after consulting with a leukemia specialist
- ✓ Consider early nephrology consultation in case of severe tumor lysis presentation

1. Abla O, Ribeiro RC. *Br J Haematol*. 2014;164(1):24-38. **2.** Abedin S, Altman JK. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):10-15. **3.** Sanz MA, et al; European LeukemiaNet. *Blood*. 2019;133(15):1630-1643. **4.** Alberta Health Services. Acute promyelocytic leukemia. Clinical Practice Guideline LYHE-008. May 2015. **5.** Mirrakhimov AE, et al. *World J Crit Care Med*. 2015;4(2):130-138. **6.** Tallman MS, Altman JK. *Blood*. 2009;114(25):5126-5135. **7.** SickKids-Caribbean Initiative. Management of children with acute leukemia and an elevated white blood cell count at diagnosis (hyperleukocytosis) in the Caribbean. Guidance Document. June 23, 2015. **8.** Giammarco S, et al. *Expert Rev Hematol*. 2017;10(2):147-154. **9.** NCCN Clinical Practice Guidelines (NCCN Guidelines®). *Acute Myeloid Leukemia*. Version 2.2020 – September 3, 2019.

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