Acute Promyelocytic Leukemia (APL)

January 5, 2017 by Josh Farkas

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Basic physiology of APL

(1) PML-RARA gene causes leukemia by blocking differentiation
- The genetic mutation causing APL is a chromosomal translocation between chromosomes 15 and 17, which results in creation of a fusion gene, PML/RARA.
  - PML is a protein normally involved in regulation of gene activity.
  - RARA is a retinoic acid receptor.
- The PML-RARA fusion gene prevents promyelocytes from differentiating into myelocytes (red X below). This renders promyelocytes immortal, allowing them to keep multiplying indefinitely and cause cause leukemia.
- Promyelocytes are angry, immature cells which wreak havoc on the coagulation system (causing disseminated intravascular coagulation).

![Diagram of differentiation and cytokine release](https://i1.wp.com/emcrit.org/wp-content/uploads/2017/01/apl2.png)

(2) administration of all-trans retinoic acid (ATRA)

- All-trans retinoic acid (ATRA) binds to the retinoic acid component of the PML-RARA fusion protein. This lifts the differentiation block, allowing promyelocytes to differentiate into neutrophils.
- ATRA has several simultaneous clinical effects:
  - (1) Differentiation of promyelocytes into neutrophils cures the leukemia (immortal, malignant promyelocytes are converted into mortal neutrophils).
  - (2) Elimination of promyelocytes eliminates the disseminated intravascular coagulation.
  - (3) The process of converting promyelocytes into neutrophils releases pro-inflammatory cytokines. This “cytokine storm” can cause a clinical picture similar to septic shock, which is known as differentiation syndrome. This can rarely cause multi-organ failure and death.

**why APL is important in critical care**
APL & the problem of early deaths

- Patients often develop unique, life-threatening problems early in the course of the disease. This leads to a unique phenomenon of "early deaths," which occur within the first month of presentation. Studies vary, but around 20% of patients may die soon after presentation. The most common causes of early deaths are:
  - Disseminated intravascular coagulation (DIC)
  - Differentiation syndrome
  - Sepsis
- If patients can avoid early death, then APL is highly curable (90%) – so patients usually have excellent long-term outcomes.
- This makes APL an ICU disease: The major barrier to long-term survival in APL is keeping patients alive for their initial ICU course. (27084953)
- Adherence to aggressive treatment protocols tailored to this disease can reduce early deaths (29033137).

epidemiology

- APL accounts for 10% of acute myeloid leukemia.
- On average, APL tends to affect younger patients than other types of acute myeloid leukemia (the median age of APL onset is 40 years old).

clinical presentation

1. APL may present similarly to other leukemias
   - Anemia (fatigue, weakness)
   - Leukopenia (infections)
2. APL has a unique tendency to cause DIC with prominent bleeding:
   - Upon presentation, nearly 90% of patients have some form of clinical bleeding (27913456).
Clinically: petechiae, bruising, intracranial hemorrhage, pulmonary hemorrhage.

**diagnostic studies**

**key diagnostic clue: DIC with hyperfibrinolysis**

- Compared to other leukemias, the extent of coagulopathy is more prominent.
- Typical coagulopathy signature of APL: (26760586)
  - Thrombocytopenia is consistently found and often severe.
  - PT is often markedly prolonged.
  - PTT is usually normal.
  - Fibrinogen is variable, but can be low.
  - D-dimer is very high (profoundly elevated D-dimer suggests APL, as opposed to other types of leukemia).

**more definitive diagnosis**

- PML/RARA PCR in blood
  - This detects the retinoic acid mutation in blood.
- Hematopathology of peripheral blood & bone marrow

**early initiation of ATRA**

**early initiation of all-trans retinoic acid (ATRA), aka tretinoin**

- ATRA should be started as soon as APL is first suspected, even before the diagnosis is confirmed.
  - The goal of early ATRA is to treat DIC (which is the leading cause of early deaths).
- ATRA has minimal toxicity (it isn't a traditional chemotherapeutic agent). So if the patient doesn't wind up having APL, it is unlikely to cause harm. However, prompt ATRA administration in patients with APL is critical to achieve control of the coagulopathy.
  - One exception to this is that ATRA is teratogenic, so it is relatively contraindicated in pregnancy.
- **Dosing of ATRA**
  - Standard dose is 45 mg/m^2 in divided doses twice daily.
  - Dose reduction to 25 mg/m^2 may be considered in patients with renal failure or side-effects (e.g. pseudotumor cerebri).

**coagulopathy of APL**

**physiology of coagulopathy in APL**

- There are two drivers of coagulopathy in APL
  - (1) Tissue factor on the surface of leukemic blasts activates the coagulation cascade.
  - (2) Annexin II on the surface of malignant leukocytes binds endogenous tPA and plasminogen, resulting in the formation of plasmin.
- The coagulopathy of APL is often called “disseminated intravascular coagulation” but this isn’t the best way to conceptualize what’s going on (DIC really just refers to #1 above).
- The coagulopathy from APL is much more malignant than most forms of DIC, because it involves prominent hyperfibrinolysis (#2 above).
  - APL patients will often behave clinically like patients who have been treated with exogenous tPA.

**risk factors for hemorrhage**

- Low fibrinogen, thrombocytopenia, elevated D-dimer, elevated PT & PTT
- WBC count >10 billion/L
- Renal failure
- Age >60 years old

[https://emcrit.org/ibcc/apl/](https://emcrit.org/ibcc/apl/)
manifestations

- Hemorrhage due to hyperfibrinolysis is the most common cause of early death
- Most deaths are due to intracranial or pulmonary hemorrhage.
- Thrombotic complications can occur, however (30803991).

management

- Usually, DIC shouldn't be treated with blood products if the patient doesn't have clinical bleeding. However, given the tendency of patients with APL to develop life-threatening hemorrhage, *pre-emptive* blood product transfusion is generally recommended.
- Transfusion targets include:
  - Platelet target >50,000/mm³
  - Fibrinogen target >150 mg/dL (perhaps most important aspect: use 10 units cryoprecipitate PRN)
  - Fresh frozen plasma as needed to target an INR below <1.5-2. European LeukemiaNet guidelines recommend targeting an INR <1.5, but this is a rather low target which may be difficult to achieve. (30803991).
- If there is any possibility of vitamin K deficiency, empiric vitamin K should be given (30423270).
- Coagulation studies should be cycled Q6hr until stable & improving.
- APL specific therapy
  - i) Immediate initiation of ATRA is fundamental to stop the underlying DIC/fibrinolysis. This should be done in all patients.
  - ii) Addition of arsenic trioxide on top of ATRA could potentially further hasten resolution of coagulopathy (27913456).
- Invasive procedures should be avoided if possible,
  - PICC line is the preferred means of obtaining central access.
  - Avoid bronchoscopy, endoscopy, arterial lines, and especially lumbar puncture.
- Tranexamic acid?
  - Supported by very scanty evidence (2567893).
  - Tranexamic acid should *not* be routinely used.
  - Tranexamic acid could be considered for a life-threatening hemorrhage, especially if it is not responding to conventional therapies or if the fibrinogen level is impossible to maintain.

**differentiation syndrome**

basics

- ATRA and/or arsenic trioxide stimulate the differentiation of promyelocytes into neutrophils. This cures the malignancy, but also unleashes a cytokine storm. Additionally, following differentiation the neutrophils may enter the tissues and cause direct tissue damage.
- About a quarter of patients will get differentiation syndrome during the first month of treatment. The risk is higher in patients with higher baseline leukocyte counts (e.g. WBC >5 billion/L).
- Differentiation syndrome accounts for ~15% of early deaths, but this may have been reduced with routine use of prophylactic steroids.

prophylaxis

- (1) Steroid
  - Remains controversial, but it is favored by many authors and study protocols (29743722).
  - Steroid prophylaxis may reduce early induction deaths due to differentiation syndrome (25302032).
  - The prophylactic steroid dose is usually prednisone 0.5 mg/kg daily until the end of induction therapy (as done in the APL046 trial) (23841729).
  - However, if the WBC count is >10,000 then higher doses may be used (e.g. dexamethasone 10 mg BID) (29033137).
- (2) Balance inputs and outputs
  - Maintain an even fluid balance.
  - Use diuretics if there is fluid retention or increased weight.

clinical features

https://emcrit.org/ibcc/apl/
• Signs & symptoms
  • Fever.
  • Peripheral edema and weight gain.
  • Pulmonary edema, pleural effusions, pericardial effusion.
  • Hypotension.
  • Rarely, neutrophil infiltration can cause skin lesions (Sweet syndrome).

• Laboratory features
  • Acute kidney injury.
  • Hyperbilirubinemia can occur.
  • WBC count rising over 10 billion/L following treatment initiation may be a feature (this often precedes or accompanies differentiation syndrome).

**differential diagnosis & evaluation**

• Common differential diagnostic considerations:
  • Heart failure
  • Sepsis
  • Diffuse alveolar hemorrhage
  • Pulmonary embolism
  • Renal failure due to another etiology (e.g. tumor lysis syndrome)

• Tests which may be considered:
  • Infectious evaluation (e.g. blood cultures)
  • Echocardiogram
  • Thoracic imaging (CXR, lung ultrasonography, possibly CT scan)

**treatment**

• Supportive care
  • Basic organ-supportive critical care (e.g. vasopressors to support blood pressure).

• Steroid
  • Cornerstone of treatment is higher-dose steroid (dexamethasone 10 mg IV Q12 hours). This should be started immediately at the earliest clinical suspicion of incipient differentiation syndrome (30803991). If this dose doesn't cause clinical improvement within a day, the dose may be increased to dexamethasone 10 mg IV q6hr (but also consider alternative diagnostic possibilities).
  • Steroid should be continued for at least three days after resolution of signs and symptoms, after which point it may be tapered off (27084953).

• Antibiotics
  • Antibiotics are *not* indicated for differentiation syndrome. However, it may be impossible to initially differentiate between differentiation syndrome and sepsis with certainty. When in doubt, it may be reasonable to cover for both possibilities (with steroid and antibiotic). Antibiotics should be stopped within <48 hours if culture results and imaging don't show a focus of infection.

• Hold ATRA and/or arsenic trioxide?
  • For mild illness, may continue these and try to treat through the syndrome.
  • For severe differentiation syndrome, stop ATRA and/or arsenic trioxide. These should be re-started after the syndrome has resolved.

• Management of ATRA- or arsenic trioxide-induced *leukocytosis*
  • Depending on the level of leukocytosis, the usual treatment is hydroxyurea (or, if this doesn't work, idarubicin). Initiating hydroxyurea if the WBC count rises >10 billion/liter could reduce the risk of differentiation syndrome (27913456).
  • Avoid leukapheresis due to the risk of precipitating fatal hemorrhage (29033137, 30803991).

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https://emcrit.org/ibcc/apl/
Sepsis is an important cause of early deaths. 
(1) If neutropenic fever occurs, this should be treated appropriately with empiric antibiotics. 
(2) Have a high index of suspicion for infection and treat aggressively if this occurs. 
- Some authors recommend empiric antibiotics for all patients with APL (29033137). This may not be necessary, but if antibiotics aren't used empirically then there should be a low threshold for aggressively investigating and treating infection.

unique complications from arsenic trioxide

Like ATRA, arsenic trioxide promotes differentiation of promyelocytes into neutrophils. This is increasingly used as a front-line agent for APL. Complications of arsenic trioxide are as follows:

Torsade de pointes

- Prophylaxis against Torsade de Pointes:
  - Discontinue other QT prolonging drugs.
  - Maintain K>4 mEq/L and Mg above 2-3 mg/dL.
  - Monitor the QT interval at least twice weekly. If the QT interval extends >500 ms, discuss with hematology whether to hold arsenic trioxide. Recent guidelines suggest that using a Bazett calculation of QTc may result in unnecessary therapy interruption due to over-estimation of the QTc, so correction using alternative rate-corrected formulas may be preferred (e.g. Fridericia, Hodges, or Sangie/Framingham) (30803991).

- Treatment of Torsade de Pointes
  - Magnesium infusion: see chapter on Torsades de pointes.

other issues

- Hyperglycemia may occur: follow glucose.
- Hepatotoxicity may occur: liver function tests should be monitored.

pseudotumor cerebri

Epidemiology
- This occurs in 3% of patients treated with ATRA.
- More common in younger patients.

Clinical presentation
- Headaches, vision changes.
- Ocular ultrasonography may be helpful in revealing elevated intracranial pressure (more on this here).

Evaluation
- Neuroimaging may be useful (including MRI if possible).
- Lumbar puncture is generally contraindicated in patients with APL and coagulopathy.

Treatments
- May include holding ATRA or reducing the dose from 45 mg/m2/day to 25 mg/m2/day (30423270).
- Other therapies may include steroid and acetazolamide.
**Acute Promyelocytic Leukemia (APL) management**

- **Basic workup & monitoring**
  - Baseline: Echo, EKG, CXR.
  - Labs: magnesium, uric acid daily.
  - CBC, PT, PTT, fibrinogen q6-8h until improved/stable.
  - D-dimer daily for the entire hospitalization.

- **ATRA**
  - Start empirically at first suspicion of APL.
  - Dose is 45 mg/m2/day, in divided doses twice daily.

- **Avoid bleeding due to hyperfibrinolysis & DIC**
  - Avoid procedures if at all possible (PICC line is preferred to central line).
  - Keep platelets >50,000.
  - Keep fibrinogen >150 mg/dl (e.g. 10 units cryoprecipitate PRN).
  - Target INR <1.5-2 if possible.

- **Avoid differentiation syndrome**
  - Maintain even fluid balance (use diuresis if weight gain or edema).
  - All patients get steroid prophylaxis.
    - Most patients: 0.5 mg/kg prednisone daily.
    - If WBC >10,000: May use dexamethasone 10 mg IV BID.

- **Avoid sepsis**
  - Treat neutropenic fever if this occurs.
  - Low threshold to investigate & treat infection.

- **Avoid tumor lysis syndrome**
  - Allopurinol 300 mg twice daily.

- **If patient is on arsenic trioxide:**
  - Keep Mg 2-3 mg/dl to reduce risk of Torsades de pointes
  - Follow liver function tests daily
  - Follow EKG & QT interval at least twice weekly
  - Discontinue QT prolonging medications

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**questions & discussion**

To keep this page small and fast, questions & discussion about this post can be found on another page here.
APL diagnosis is a medical emergency. All patients may not require ICU admission, but hospital admission and careful laboratory monitoring is mandatory.

- Don't underestimate DIC due to APML. This is much worse than most types of DIC. The first manifestation can be lethal intracranial hemorrhage.
- Complications encountered in these patients are often predictable (e.g. APL differentiation syndrome, Torsade de points from arsenic trioxide). Aggressive management may avoid these issues entirely or allow for prompt treatment.

**Going further:**


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