Aplastic Anemia

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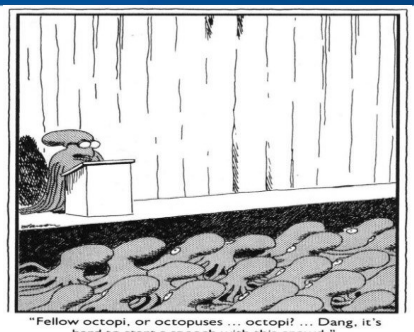
Diagnosis of aplastic anemia
Lots of terms, all understandable!



"Fellow octopi, or octopuses ... octopi? ... Dang, it's hard to start a speech with this crowd."

Diagnosis of Aplastic Anemia

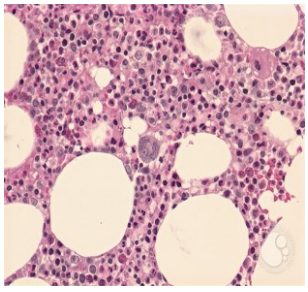
- **Hematopoietic stem cell disorders**
  - **Includes AA, MDS, AML, PNH**
- **Associated with marked reduction in bone marrow cellularity**
- **With deficient blood cell production (bone marrow failure)**
- **It is the combination of low counts with marked reduction in bone marrow cellularity that distinguishes aplastic anemia from other bone marrow failure syndromes.**

Normocellular Bone Marrow Biopsy

Cellularity

The % of bone marrow occupied by cells

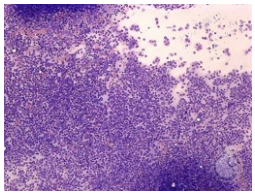
Normally about 1/3-1/2



Hypercellular Bone Marrow Biopsy

Patient with MDS

Bone marrow with 80-90% cellularity AND

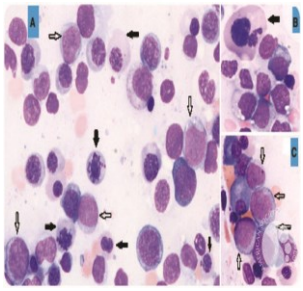


MDS Bone Marrow Biopsy

Usually hypercellular bone marrow

AND

Funny looking (dysplastic cells)

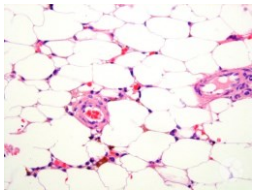


Hypocellular Bone Marrow Aplastic Anemia

Cellularity here <5%

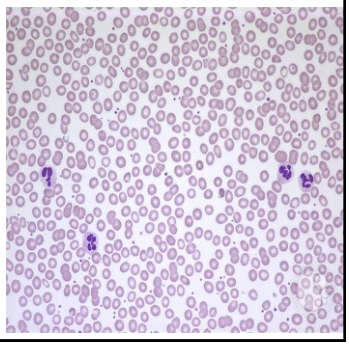
Diagnostic criteria is <30%

Bone marrow cellularity can be spotty and doctor may want to repeat bone marrow to verify low cell count



Normal Blood Smear

- **Many neutrophils**
- **Infection fighting cells**
- **Platelets readily identified**



Pancytopenia in Aplastic Anemia

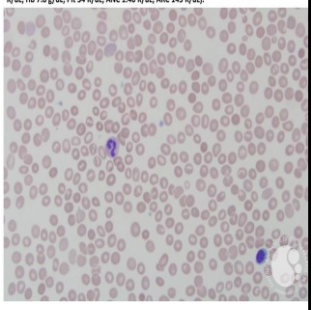
Results in disease complications

Severe AA: 2 or 3/3
- ANC<500/µL
- Platelet<20,000/µL
- Red cell transfusion dependent with low retic count

Very Severe: ANC<200/µL
- THIS is the really critical neutrophil count

Moderate
- Depression 2/3 counts
- Do not meet above

Paroxysmal nocturnal hemoglobinuria (PNH). 28 year old male with pancytopenia (WBC 3.3 K/uL, Hb 7.8 g/dL, Plt 34 K/uL, ANC 1.40 K/uL, ARC 145 K/uL).



Classification Based on Cause

- **Acquired Aplastic Anemia (not born with)**
  - **Primary (cause is not apparent)**
    - **Idiopathic aplastic anemia: >70-80%**
    - **Aplastic anemia/PNH syndrome**
  - **Secondary**
    - **Drug associated: NSAID such as Indocin>uncommon**
      - **Benzene is classic**
    - **Viruses>uncommon**
    - **With autoimmune disease such as Lupus, RA**
- **Inherited Bone Marrow Failure Syndromes**
  - **Dyskeratosis congenita**
  - **Fanconi's anemia**

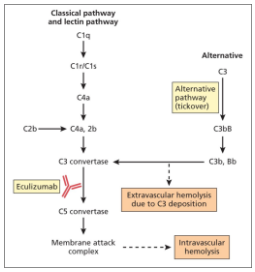
"Idiopathic/Primary Aplastic Anemia" An Autoimmune Disorder

Thomas ED, Storb R, Giblett ER, Longpre B, Weiden PL, Fefer A, Witherspoon R, Clift RA, Buckner CD: Recovery from aplastic anemia following attempted marrow transplantation. Exp Hematol 4:97-102, 1976

- **Patients were given ATGAM to prevent rejection**
- **Several rejected anyway…BUT RECOVERED COUNTS**
- **First evidence for "autoimmune" cause for aplastic anemia**
- **Subsequently proven with ATGAM alone**
- **By far most common type of AA**

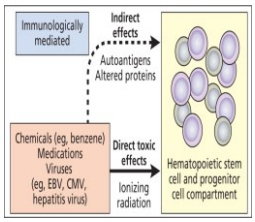
Classification Based on Cause PNH and Aplastic Anemia

- **Complement**
  - **"Complements" immune system**
  - **Kills bugs and damaged cells**
  - **"PIGA" makes anchor that attaches inhibitory proteins to blood cells**
  - **Mutations knock out function and results in activation of complement and killing of blood cells**
  - **Autoimmune attack increases PNH cells in blood**



Classification Based on Cause Drugs and Viruses

- Some can kill stem cells directly without involving immune system
- Increasingly recognized that drugs/viruses could also lead to activation of immune system
- For patients with severe AA, wait 1-2 weeks to do viral studies or wash out drugs
- Then proceed to treat



Classification Based on Cause Congenital Aplastic Anemia

- Congenital=Born with
  - Mutations present at birth
  - Pts may report other effected family members
- Why important
  - Don't respond to ATGAM
  - Donors may have same thing
- Dyskeratosis congenita
  - "Telomeropathy"
  - >10 different mutations
  - Shortened telomeres
  - Blood cells die as a result
  - Abnormal pigmentation, leukoplakia, abnormal nails
- Treatment: Bone marrow transplant
  - Thought not to be immune

Problems with Classification Not This Simple

- Same as in DC can be seen only in blood cells-(somatic)
  - Occur in 10% of patients with "Idiopathic" AA
  - No family history. No physical changes
  - Some respond to ATGAM
- NGS (DNA analysis)>>Better understanding of AA
  - Acquired mutations in one of three
  - Some are seen in AML/MDS
    - ?Marker for later change to AML/MDS
  - Some may be markers for response to ATGAM

Problems with Classification Not So Simple

- Hypocellular MDS
  - MDS usually HYPER cellular
  - Low cellularity, funny looking cells
  - Certain chromosome changes indicate
  - Managed with transplant
  - BUT some do respond to ATGAM
  - Role of autoimmunity in some pts with MDS

Classification of Aplastic Anemia

Type	Idiopathic	AA/PNH	Congenital	Drugs/Virus
Age	-Young adults -Pts>60 yo	Similar to AA	Usually <20 Can occur up to 50 yo	Any
Physical findings	No	No	Often	No
Family history	No	No	Often	No
Proportion All AA	Large majority	Uncommon	Uncommon	Rare
Respond to ATGAM	70-80%	AA yes PNH no	No	No (rare)
Chromosome changes	Uncommon	Uncommon	Some pts	Some drugs
DNA Mutations All Cells	No	No	Yes	No
Comment	Caution: Hypocellular MDS	PNH + cells usually low nos	Require transplant	(+) tests EBV, parvo, CMV

Conclusions
Diagnosis and Classification

- **Diagnosis: Low blood counts with reduced cellularity of bone marrow**
- **Most patients (Primary AA) respond to ATGAM indicating "autoimmune"**
  - **Incidence is 0.2/100,000**
  - **AML and MDS> 10 times more common**
  - **Mutations in 1/3 may predict response to treatment**
- **PNH can coexist with AA and when this is true blood counts improve with ATGAM. PNH less severe than severe PNH.**

Conclusions
Diagnosis and Classification

- **Drugs and viruses are a rare cause of aplastic anemia and some of these may be autoimmune**
- **Congenital aplastic anemia is caused by gene mutations present in all body cells and often with physical findings or family history. BMT is treatment of choice. Low threshold for testing since transplant can be more risky.**

Patient #1

64 year old man presented July 2015 with fatigue and "rushing" sound in his ears. No fevers and no family history of AA/MDS/AML. Eats a regular diet.

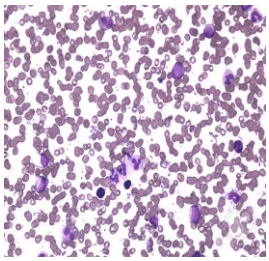
No medical issues. Normal CBC as part of routine H/P in December of 2014. NO medications since February.

Hemoglobin 6.1 and received 3 units of blood with improved symptoms. Went on to receive platelets weekly, blood every other week. Creatinine, lft's normal.

In September: WBC 2.3, ANC=400, platelets=5000 and hgb 8.7 and retic<2%. No blasts or abnormal WBC.

A bone marrow was performed.

Which Blood Smear



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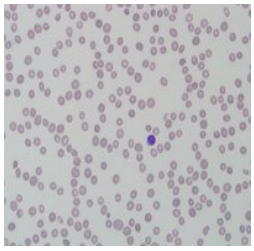
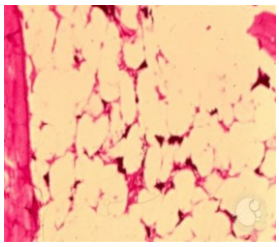


B

Which Bone Marrow



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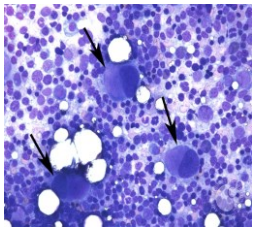


B

Patient #1 Bone Marrow

- DIAGNOSIS:

  A. BONE MARROW BIOPSY AND ASPIRATE (REVIEW OF 15 OUTSIDE SLIDES, BM15-562): HYPOCELLULAR MARROW WITH ERYTHROID PREDOMINANCE AND MARKED MYELOID HYPOPLASIA. (SEE COMMENT)
  THERE IS NO OVERT MORPHOLOGIC EVIDENCE OF LYMPHOMA OR ACUTE LEUKEMIA.

  COMMENT: The peripheral blood smear shows pancytopenia with morphologically unremarkable white blood cells and no increase in circulating blasts. The bone marrow aspirate smears are paucispicular and markedly hypocellular with decreased multilineage hematopoiesis. The myeloid precursors are markedly reduced in number and the cellular elements are predominantly maturing erythroid elements with mild megaloblastoid features. Megakaryocytes are markedly decreased. Lymphocytes and plasma cells are not increased. The bone marrow core biopsy contains patchy areas of cellular marrow particles that are 0-50% cellular with overall cellularity of 10%. Per outside report, cytogenetic analysis showed a normal male karyotype."

Patient #1

1 healthy full sibling.

Haptoglobin/LDH normal (no evidence of hemolysis)

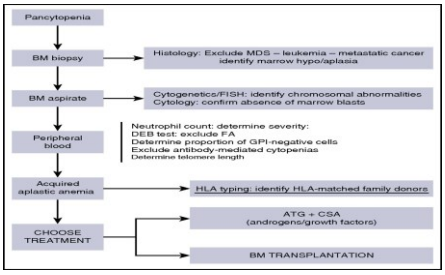
B12 and folic acid normal. DEB test was negative, rules out Fanconi's.

Testing for PNH with <1% red cells and white cells lacking CD55/59 c/w a very small population of PNH cells.

HLA typing done for possible transplant

Diagnosis: Primary aplastic anemia, severe with small, insignificant PNH clone.

Diagnostic Evaluation in Patient With Low Blood Counts

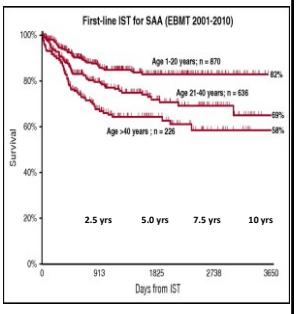


Patient #1 Treatment

- **Received filtered blood products to reduce risk of antibodies to platelets/RBC AND to reduce risk of rejection if transplanted.**
- **Given antibiotics to prevent viral and bacterial infections.**
- **Admitted and treated with ATGAM daily for 4 doses given with high doses of steroids and cyclosporine.**
- **With first dose fevers and hives. Did not recur.**
- **Discharged day after completion for outpatient follow-up.**

ATGAM/CSA: Immunosuppression

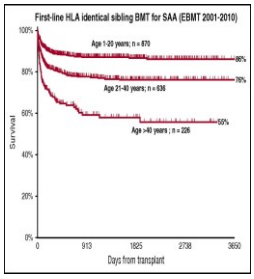
- **Response in ≈70%**
  - Time to respond=2-3 mos
  - Can be as late as 6 months
  - Lower in older, very severe
  - Relapse in 1/3 by 5 years
  - Must slowly taper CSA
- **What to do in relapse**
  - Many respond to CSA only
  - If fail, consider 2nd ATGAM
  - Total about 60% respond
- **Late MDS in 20%**
  - Can happen over 10 yrs
  - Cause for late drop in survival
  - BMT is usually only approach

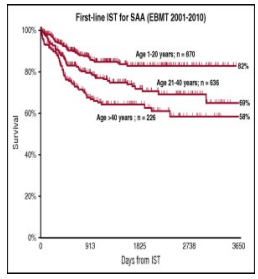


Stem Cell Transplant (BMT)

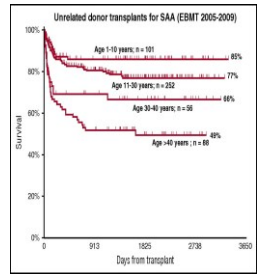
- **Up to age 60>>CURES most patients**
- **Advantages**
  - **Rapidly restores blood counts (w/in 20-30 days BMT)**
  - **Relapse of disease very uncommon**
  - **Lower risk of late MDS**
- **Disadvantages**
  - **About 5% reject>>often fatal**
  - **GVHD is THE major cause of death**
    - **Occurs in most patients**
    - **Causes long term medical problems**
    - **Fatal in 10-30% patients**
    - **Risk is age and match dependent**

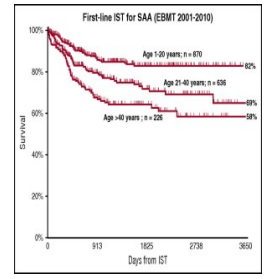
Treatment of Severe Acquired AA
ATGAM/CSA versus Matched Sibling Transplant





Treatment of Severe Acquired AA
ATGAM/CSA versus Unrelated Donor





Treatment of Aplastic Anemia
ATGAM/CSA vs Transplant

- **First line of treatment: Balance risk of transplant with effectiveness of ATGAM/CSA**
  - **<40 and matched sibling>Transplant**
  - **>40 or no matched sibling>ATGAM/CSA**
- **Some would transplant older, healthy patients matched sib**
  - **If very severe, strong consideration**
  - **Higher risk of late MDS in pts>60**

Treatment of Aplastic Anemia
ATGAM/CSA vs Transplant

- **Second line of treatment If ATGAM/CSA not effective 4-6 mos**
  - **Donor available: Sibling or unrelated donor**
    - **If healthy, transplant up to age ??**
    - **If not healthy, options as for patients without donor**
  - **No matched sibling or unrelated donor**
    - **Second ATG/CSA**
    - **Eltrombopag**
    - **Androgens with CSA**
    - **Haplo transplant (If very very healthy)**

Conclusions
Treatment of Aplastic Anemia

- ATGAM and CSA produces remission in large majority of patients with aplastic anemia. Advantage: low toxicity. Problems: takes 2-3 months to work; frequent recurrence; late AML/MDS
- BMT produces remission in large majority of patients. Advantage: rapid normalization counts; disease cured without late AML/MDS; can cure congenital AA; Disadvantage: risk of death 20-40% depending on age; GVHD can last for years and cause disability.
- Patients with matched siblings less than age 40-60 should proceed with transplant.
- Older patients and those without matched siblings should first get ATGAM/CSA and use transplant if fails.
-

Patient #1
Post ATGAM/CSA Course

- CSA taper initiated at 8 months
  - WBC 3.6/ANC 1.8/hgb 13.0/platelets 78,000
  - Memory problems ?CSA
  - Tapered CSA from 100 bid to 100 daily
- 2 months later platelets drop to 40,000
  - CSA dose increased
- 1 month later platelets drop to 28,000
  - Dose increased again
- Last platelet count 34, 000

The Future
There is Great Hope!!

- Improved control of GVHD, better antibiotics and improved typing will improve the outcome of transplant. likely be comparable (may be superior) to unrelated donor so that donor will be available for most patients.
- New more effective immunosuppression. Example: combination of eltrombopag with ATGAM/CSA.
- DNA analysis will tell us why the immune system attacks bone marrow. Drugs that reverse effect of mutation would be more effective and less toxic.
- Mutations will be identified that predict development of MDS or acute leukemia leading to early transplant in these patient.

Patient #2

- 24 year old man
  - Dec 2013 easy bruising and low platelet count
  - Given prednisone with "improvement"
  - No family history of blood or marrow disorders
  - June 2015: WBC 1.1, hgb 4.6, platelet 1
  - Bone marrow 15% cellular without dysplasia
  - Normal cytogenetics; 6% PNH cells; negative Fanconi
  - Received weekly blood and platelets

Patient #2

- 24 year old man with probable primary aplastic anemia
  - Siblings not matched
  - Has matched unrelated donor
  - Jehovah's witness, wanted to minimize transfusions?
  - How should we treat?

Patient #2

- 24 year old man with probable primary aplastic anemia
  - Admitted and received high dose chemotherapy/total body radiation with ATGAM. Transplant October 2015.
  - Fungal infection lungs while counts low.
  - Severe mouth pain from chemotherapy
  - 20 days after transplant: ANC>500, platelets 100,000
  - Given prednisone for GI GVHD, improved.
  - 6 week hospital stay; remained in Gainesville for 2 months.

Patient #2

- 24 year old man with probable primary aplastic anemia
  - December of 2016: SOB and diagnosis of lung GVHD treated with steroids.
  - Slow improvement
  - Currently
    - Normal blood counts, no transfusions
    - On multiple medications. Antidepresants
    - Weak and unable to work, but improving

Patient #2

- 24 year old man with probable primary aplastic anemia
  - Good: Rapid count recovery with minimal risk of disease returning and minimal risk of late MDS or AML
  - Not so good: Disabled due to GVHD, but recovering. Taking multiple meds with side-effects.

END Aplastic Anemia

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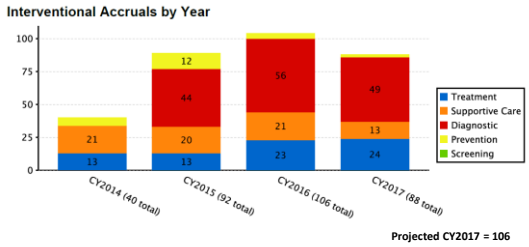
University of Florida
College of Medicine

UFHealth
UNIVERSITY OF FLORIDA HEALTH

Who Are We?

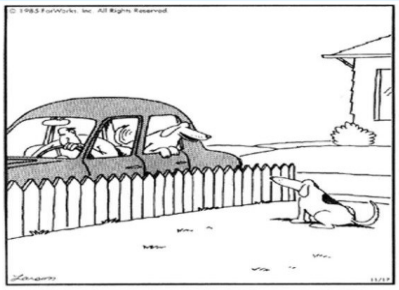
- 10 physicians board certified in Hematology/ Oncology with 7 having >10 years experience.
- 24 bed transplant unit and 24 bed ward to treat leukemia and lymphoma.
- Comprehensive care of patients with leukemia, MDS, lymphoma, bone marrow failure, pediatrics. Standard therapy and transplant
- Survival after donor transplants best in state.
- Very active in clinical trials for both leukemia and transplant.
- Weekly clinic at UF Health/Orlando. Its worth the drive!!

Our group leads UFHCC in enrollment to interventional clinical trials CRITICAL FOR CANCER CENTER DESIGNATION!!!



Projected CY2017 = 106

Why We Must Learn to Listen



"Ha ha ha, Biff. Guess what? After we go to the drugstore and the post office, I'm going to the vet's to get tutored."