Aplastic Anemia-Understanding Your Disease and Treatment Options

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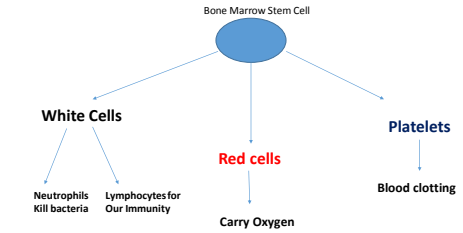
Case Presentation

- 47 y/o woman, who was previously very active, who presented to her PCP with complaints of shortness of breath on exertion, fatigue, dizziness and nose bleeding.
- She typically runs 4-5 miles per day and hikes or skis on her days off. Over the last 2 months she has noticed that it has been more difficult to run that distance. Now, she can barely run a few blocks. She also gets winded walking up 1-2 flights of stairs. The nose bleeds started 1 week ago.
- Her past medication history is notable for heartburn/GERD, improved with Prilosec.
- She has never undergone a surgery
- Besides the Prilosec, she also takes oral contraceptive pills to minimize her periods.
- Diabetes runs in her family. She has no family history of blood problems.

Case Presentation

- Her PCP checked her blood counts: White count was critically low at 1.2 (normal 4.5-10), hemoglobin was critically low at 5.6 (normal 11.5-13.5), hematocrit was critically low at 16.5% (normal 34-40%), and platelet count was critically low at 5 (normal 150-450).
- She was referred to her local emergency room for further management.

How are blood cells made?



Work-up of low blood counts-Pancytopenia

Blood counts can be low for a variety of reasons:

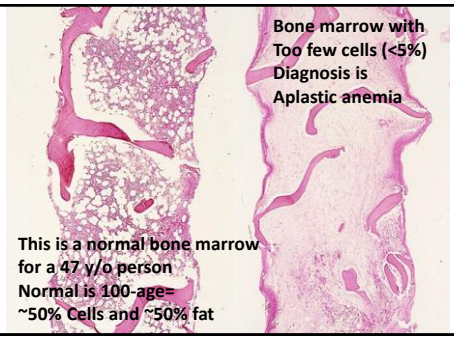
-nutritional defects-in particular deficiencies of copper, folic acid and vitamin B12
-hormone deficiencies-thyroid in particular and testosterone in men
-reaction to medications
-autoimmune diseases-like rheumatoid arthritis or lupus
-suppression from viruses
-genetic predisposition to low blood counts
-bone marrow damage from toxins or radiation
-bone marrow stem cell defect (myelodysplastic syndrome–MDS)
-cancer (either leukemia or other cancers that have invaded the bone marrow)

Evaluation of Pancytopenia

- Peripheral blood testing to evaluate for nutritional deficiencies, including a serum copper level, homocysteine level and methylmalonic acid
- Review of the peripheral smear to look for atypical lymphocytes or peripheral blood flow cytometry to t/o lymphoproliferative disorder.
- Serum protein electrophoresis, basic chemistries, including liver function tests, ANA, rheumatoid factor, TSH and testosterone level (in males)
- Peripheral blood testing for PNH using high sensitivity flow cytometry
- Blood breakage testing and Telomere length testing
- Bone marrow biopsy and aspirate with flow cytometry, cytogenetics, FISH for the common translocations found in AML and MDS and molecular testing for the common mutations found in MDS and AML.

Evaluation of Pancytopenia

- A good work-up includes blood tests and a bone marrow biopsy to evaluate for:
  - Infections
  - Nutritional or hormone deficiencies
  - Evaluate for signs of stem cell damage (myelodysplastic syndrome (MDS) or leukemia)
- The diagnosis of aplastic anemia is made when:
  - Bone marrow cells are much less than they should be
  - No other cause for this-no evidence of infection or nutritional deficiencies
  - No evidence that the stem cells are mutated/dysplastic-no evidence of MDS or leukemia.



Diagnosis of Aplastic Anemia

- Bone marrow cellularity is too low
- No evidence of damage or mutation to the stem cell pool
  - Chromosome analysis shows no chromosome abnormalities
  - FISH shows no abnormalities seen in MDS/AML
  - Mutational analysis shows no significant gene mutations
- The diagnosis of aplastic anemia doesn't tell you *the cause*
- Aplastic anemia can be nonsevere/moderate, severe or very severe-this guides treatment planning and prognosis
- Severity of the aplastic anemia depends on the counts:
  - Absolute neutrophil count (ANC)=total white cell count X % of neutrophils
  - Severe aplastic anemia: platelet count <20,000 and ANC <0.5 (or 500)
  - Very severe aplastic anemia: platelet count <20,000 and ANC <0.2 (or 200)
  - Non-severe or Moderate aplastic anemia: does not meet the criteria for severe aplastic anemia

Aplastic Anemia

- In western Europe/US the incidence is 2-3 per million/
- The rates are double this in Asia
- The incidence between males and females is equal, although this may differ depending on location and age
- The ages where this is most common include ages 15-24 and those greater than age 45
- The highest incidence is in patients greater than age 65
- In this study they found that 28.5% of patients had been exposed to drugs or toxic agents felt to be the cause of the aplastic anemia
- Approximately 2/3 the of cases had severe or very severe disease

Montaine E, Epidemiology of aplastic anemia: a prospective multicenter study. Haematologica, 2008

What causes aplastic anemia?

- Some people have an inherited predisposition to developing aplastic anemia. It is important to identify these people
- Acquired aplastic anemia: The most common cause is idiopathic aplastic anemia. This is when the immune system is triggered to attack the bone marrow stem cells
  - Driving force for this dysregulated immune response is not clear
  - Balance between attack and protect is skewed
  - T cells are the bad guys (specifically CD8+ cytotoxic T cells)
- Inherited aplastic anemia: The bone marrow stem cells are weak and are not able to recover from stressors
  - In these diseases the risk of developing blood cancers is very high
  - It is important to screen all patients for these disorders
  - Inherited defects may be more common in younger patients with physical abnormalities or those with a family history of cancers, liver or lung problems.

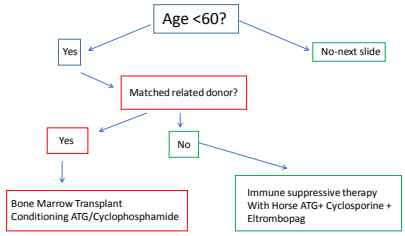
Inherited vs. Acquired

- Important to identify patients with an inherited defect causing aplastic anemia.
- Impacts the decision regarding
  - Treatment-we choose specific treatments for inherited vs. acquired aplastic anemia
  - Finding a donor for bone marrow transplant-family members would need special screening
  - Risk of cancers-risk of blood cancers and other cancers much higher with inherited diseases

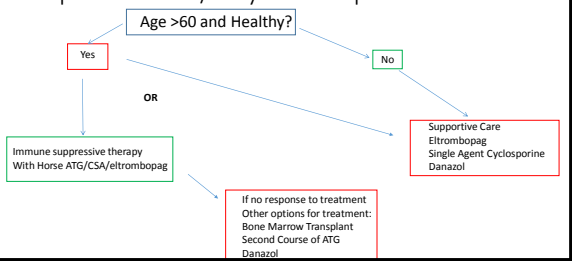
Case Presentation

- The patient was provided platelet and blood transfusions to improve her anemia and reduce her bleeding risk
- She underwent peripheral blood and bone marrow testing
- Her bone marrow had a cellularity of 5-10%, with no evidence of dysplasia.
- Peripheral blood testing revealed no inherited causes of aplastic anemia.
- She was referred urgently for evaluation for a bone marrow transplant.

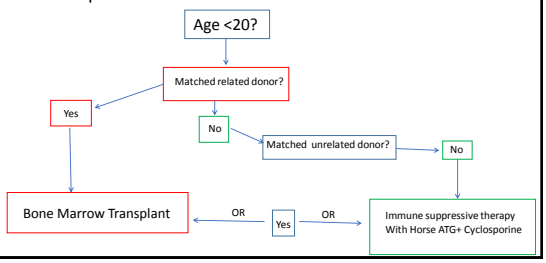
Treatment approach for acquired Severe/Very severe aplastic anemia



Treatment approach for older patients with acquired Severe/Very severe aplastic anemia



Treatment approach for acquired Severe/Very severe aplastic anemia



Treatment Recommendations-History

- First reports of successful treatment with splenectomy (1940's-)
- Some cases of response noted with the use of prednisone (1950's) and anabolic steroids (1960's)
- 1960's bone marrow infusions were noted to have some responses
- Major progress was made in the 1980's with antithymocyte globulin (50% response) and recognition that the immune system was targeting the bone marrow cells
- Response rates were enhanced with the addition of cyclosporine to antithymocyte globulin (60+% response)
- Most recently, the addition of eltrombopag to ATG/cyclosporine shows promise of adding an additional 10+% to initial response rates.

About ATG (Anti-thymocyte globulin)

- Thymocyte=T cell
- Horses or rabbits are exposed to human T lymphocytes, and the serum is collected, purified and sterilized.
- Binds a wide variety of proteins on the surface of lymphocytes and tags them for destruction
- Because it is a foreign animal protein, the main risks of infusion include allergic reactions and serum sickness.
- Rabbit ATG has the same risk as far as allergic reactions. More potent (dose $1/10^{th}$ dose of horse ATG).
- ATG is most effective when combined with an additional immune suppressant (cyclosporine)

Horse vs. Rabbit ATG

Rabbit ATG	Horse ATG
First choice for use in bone marrow transplant regimens	First choice for initial treatment of aplastic anemia
Can be given in patients that have a serious allergic reaction to horse ATG	Skin test must be given prior to full dose administration. Cannot use if + skin test reaction
Patients that fail first round of horse ATG may respond to follow-up treatment with rabbit ATG	A second round of therapy is typically not given for those patients that don't respond to first round

Cyclosporine

- Cyclosporine is an immune suppressant that impacts T cell activity
- This pill is typically taken twice a day, around 12 hours apart.
- Cyclosporine has of goal range-we want blood levels within a specific range to optimize the effectiveness and reduce side effects
- Cyclosporine comes into formulations a modified formulation and normal.
  - Modified formulation is most commonly used because of improved absorption. Common trade names include Gengraf and Neoral
  - The unmodified formulation is Sandimmune
- Side effects of cyclosporine include nausea, muscle cramping, headaches, taste changes, electrolyte imbalance, high blood pressure, kidney problems, elevated liver tests, and an increased risk of infection.
- Cyclosporine has a number of drug interactions, which can change your blood levels and increase the risk of side effects

Eltrombopag

- Eltrombopag is a thrombopoietin (TPO) receptor agonist
- It is a pill that you take once a day on an empty stomach.
- This drug stimulates TPO-TPO is important in stimulating platelet production as well as bone marrow stem cell growth.
- This drug was originally designed to treat patients with immune associated thrombocytopenia
- The team at the NIH tried this drug on aplastic anemia and found it was successful in patients who did not respond to immune suppression
- Because of its overall good tolerance, they investigated integrating it into initial immunosuppressive therapy, with initial reports showing a 10% improvement and response rates
- The side effects associated with this drug include GI upset, diarrhea, liver function test abnormalities.

Case Presentation

- Pursued typing of the patient and her sister-NO match.
- Patient had very common typing, therefore pursued typing of her parents-NO match
- Therefore, proceeded with horse ATG and cyclosporine (CSA)

Supportive care for AA

- All blood products must be radiated and filtered. This is to remove the donor immune cells from the product.
- Platelet transfusions for platelet count <10 or active bleeding
- Red cell transfusions for hematocrit <21% (even less if tolerated) or symptoms of anemia
- We try to limit transfusions to reduce the risk of iron overload and formation of antibodies against platelets
- Antibiotics are important to prevent infections when the ANC is low and prompt recognition and treatment of infections is critical.

Supportive care for AA

- Antibiotic use to prevent infections is critical in those patients with an ANC <500 (0.5)
- Levofloxacin to prevent bacterial infection
- Acyclovir or valacyclovir to prevent shingles and cold sores
- Posaconazole, voriconazole, isavuconazole are broad spectrum azoles to prevent severe fungal and mold infections. These are recommended rather than fluconazole to prevent these serious infections.
  - These drugs, while highly effective, are very expensive
  - There are typically medication assistance programs from the company to help support you getting these medications
  - These drugs all interact with cyclosporine, and therefore cyclosporine dosing has to be reduced at least in half typically when these medications are used
- Prompt recognition of an infection and seeking medical care is very important

Supportive care for AA

- What are the things we worry about with continued need for transfusions?
  - The development of antibodies, making it more difficult to find red blood cell product for you
  - The development of antibodies against platelets, which reduces the response to platelet transfusions
  - The development of iron overload due to red cell transfusions
- You should speak to your doctor about options for reducing the risk of iron overload

Case Presentation #1

- The patient required antibiotics, platelet and red cell transfusions for the first 3 months after ATG treatment.
- After around 12 weeks her platelet count stayed about 10 without a platelet transfusion
- After 6 months after treatment she no longer required red cell transfusions and her platelet count was around 50.
- She is now just over 2 years from treatment and her counts are near normal
- She is on a slow cyclosporine taper schedule, which she is tolerating well.

Immunosuppression for Aplastic Anemia

- Atgam (horse ATG) is our first choice in the US (due to reports by the NIH team of improved response with horse vs. rabbit)
- Response rates estimated at 60-70% (maybe more with the addition of eltrombopag)
- ATG requires a 5 day hospital stay for the infusion to be given (the dosing is typically once a day for 4 days total)
- ATG should always be given at a facility that has experience giving this agent due to complications with the treatment
- Cyclosporine is initiated on the same day as the ATG, with goal levels typically in the range of 250-400, based on tolerance and side effects.
- Patients typically require outpatient visits 2-4 times per week for monitoring of blood counts electrolytes and kidney function liver function tests and blood product support.

Immunosuppression for Aplastic Anemia-post treatment follow-up

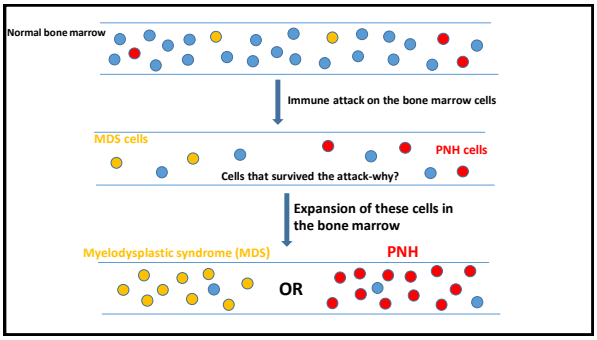
- For those patients that achieve transfusion independence, we ultimately would like to try to taper them off the immune suppression.
- What are the concerns for patients who have received immune suppression?
- Relapse
- Long-term impacts of immune suppression
- Secondary clonal disorders

Case presentation #2

- 36 y/o male was diagnosed with severe aplastic anemia after presenting with easy bruising and fevers.
- Treated with horse ATG and cyclosporine with good response, developed transfusion independence, but without normal counts.
- About 6 months after the treatment was started, his cyclosporine was discontinued due to improvement in counts.
- Patient presented for evaluation 3 years later with fatigue, and blood counts found all his blood counts to be low and he required a red cell transfusion.
- What can cause low blood counts in this patient?

Cause of low blood counts in AA patients previously treated

- Disease relapse-the immune system starts to attack the bone marrow stem cells again
  - Higher risk in patients who have a rapid immune suppression taper
- New problem-nutritional defects, viral infections or hormone problems
- New problem-myelodysplastic syndrome (MDS) or acute leukemia.
- New problem-PNH-paroxysmal nocturnal hemoglobinuria



Problems after treatment with immune suppression

- Relapse
  - In studies following patients status post ATG the risk of relapse is around 30-40%
  - This risk can be reduced to <10% with very slow cyclosporine tapers (0.3-0.7mg/kg/month) with many patients being dependent on cyclosporine (15-25%)
  - Early relapse can often be captured by increasing or reinstituting cyclosporine alone.
- Secondary clonal disorders
  - Includes PNH, MDS, acute leukemia
  - Estimated risk through long-term studies around 20+%, with the risk remaining throughout life

Case presentation #2

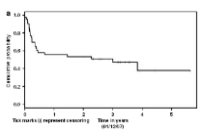
- Bone marrow biopsy performed, showing evidence of MDS, with adequate cellularity, dysplastic features, and clone with monosomy 7.
- Therefore, he was diagnosed with MDS
- Referred to me for additional treatment considerations.

Case presentation #2

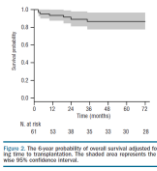
- Typing found that his brother was a fully matched sibling.
- Proceeded to transplant to treat his MDS
- Doing really well to date….with normal blood counts.
- He is recovering from the effects of bone marrow transplant

Outcome for BMT is better for AA than MDS

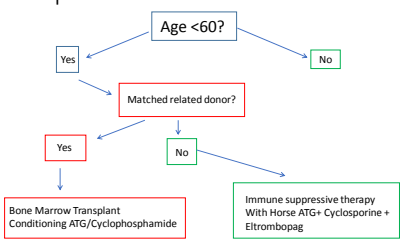
Typical results for BMT for MDS/AML-At 5-10 years after transplant the rate of survival is around 40%.



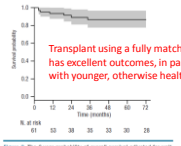
BMT for Aplastic Anemia using a sibling donor-At 5-10 years after transplant the rate of survival is around 90%



Treatment approach for acquired Severe/Very severe aplastic anemia

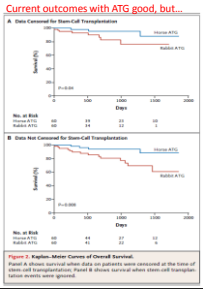


Why these recommendations?



Transplant using a fully matched sibling has excellent outcomes, in particular with younger, otherwise healthy patients.

Current outcomes with ATG good, but…



There are problems after ATG
-Relapse of aplastic anemia
-dependence on cyclosporine
-development of a new blood problem (like PNH, MDS or leukemia)

Patient presentation #3

- This is a 28-year-old gentleman who is transferred to our center with pancytopenia and concern for MDS
- He presented to his primary care physician with symptoms of a pneumonia, which failed an initial course of antibiotics.
- He was discovered to have severe pancytopenia and evidence of an atypical pneumonia. He was transferred to our facility for further management.
- A bone marrow biopsy was performed, which showed evidence of MDS with an elevated blast count.
- He had no family history of blood disorders, liver problems, lung problems, although his father was an alcoholic.

Patient presentation #3

- Because this patient was very young for the diagnosis of MDS we pursued a workup for inherited marrow failure disorders.
- Peripheral blood breakage testing revealed that the patient had Fanconi anemia.
- He was treated with azacitidine with benefits in his counts.
- He proceeded to a bone marrow transplant with a matched unrelated donor.
- Post transplant complications included squamous cell carcinoma of his tonsil.

Inherited Marrow Failure Work-up

- Inherited marrow failure should be considered in any young patient with aplastic anemia or MDS
- Initial work-up should include
  - Blood breakage testing for Fanconi Anemia
  - Telomere length testing for dyskeratosis congenita or other telomere maintenance disorders
  - Other considerations based on clinical factors-physical deformities, pancreatic insufficiency, red cell dependence, preceding thrombocytopenia.

Why is it important to identify Inherited Aplastic Anemia?

- Treatment-we choose specific treatments for inherited vs. acquired aplastic anemia
- Finding a donor for bone marrow transplant-family members would need special screening to look for the same defect.
  - In the case of this patient, his brothers were not a match. However, we did screen them for Fanconi Anemia.
- Risk of cancers-risk of blood cancers and other cancers much higher with inherited diseases.
  - WE found his tonsil cancer on routine screening before he had symptoms.

Management of Inherited AA

- Poor response rates to immune suppressive therapy
- Respond well to Danazol frequently-first choice of agents
- The risk of clonal evolution to MDS or leukemia is very high
- For MDS/clonal evolution transplant is required
- Transplant conditioning should be altered significantly to reduce toxicity
- Potential sibling donors need to be screened for asymptomatic disease

Questions?