Pure Red Cell Aplasia Secondary to Immunosuppressive Agents in Heart Transplant Recipient

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Background

- PTA(post-transplant anemia) is a prevalent sequela of sold organ transplantation and a potential independent risk factor for cardiovascular morbidity and mortality.

(Blosser et al. Transplantation review, 2010)

- **Causes of PTA**

Decreased RBC production	Increased RBC destruction
drug-induced aplasia	immune-mediated hemolysis
immunosuppression	passenger lymphocyte syndrome
ATG	immunosuppression
azathioprine	ATG
MMF	intravenous Ig
sirolimus	PTLD
renin-angiotensin-aldosterone system blockade	migroangiopathic hemolytic anemia
ACEIs	tacrolimus
ARBs	cyclosporine
antimicrobial agents	sirolimus
ganciclovir	nonimmune hemolysis
trimethoprim-sulfamethoxazole	glucose 6-phosphate dehydrogenase deficiency
erythropoietin deficiency	dapsone
allograft dysfunction	trimethoprim-sulfamethoxazole
erythropoietin resistance	hemoglobinopathies
iron deficiency	Loss of RBCs
hyperparathyroidism	surgical blood loss
infections	gastrointestinal blood loss
parvovirus B19	frequent phlebotomy
cytomegalovirus	
EBV	
HIV	
folate and B_{12} deficiency	
marrow infiltrative disease	
PTLD	
aplastic anemia	

Case

C.C : Dyspnea and dizziness since 1 month ago

P.Hx. :

s/p Pacemaker insertion d/t complete AV block (2010.8)

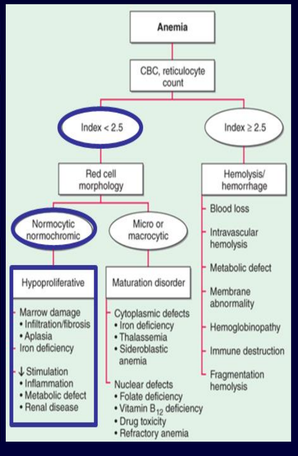
s/p Heart transplantation (2016.12) d/t giant cell myocarditis, 3 months ago and post-op acute kidney injury (on steroid, MMF, tacrolimus)

Lab. findings :

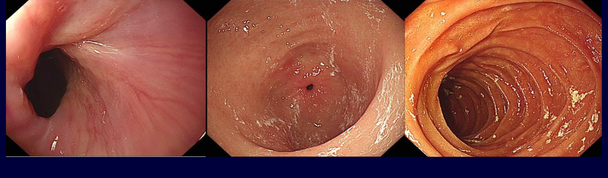
1) normocytic normochromic anemia

2) severe reticulopenia

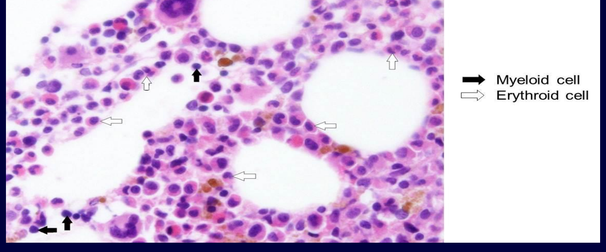
Lab	Value	Normal range
WBC	5000/uL	4000~10800/uL
Hb	5.3g/dL(↓)	11.7~16.0g/dL
Patelet	132k/uL(↓)	150~400k/uL
Reticulocyte production index (RPI)	0.47(↓)	
MCV	92.7fL	80.0~98.0fL
MCH	29.9pg	27.0~33.0pg
PB smear	(-)	
EPO	552mIU/mL (↑)	4.3~29mIU/mL
VitB12	944pg/mL	180~947pg/mL
Folate	5.86ng/mL	3.1~19.9ng/mL
Serum Iron	236ug/dL(↑)	40~158ug/dL
TIBC	272ug/dL	271~435μg/dL
Ferritin	891ng/mL(↑)	11~306.8ng/mL
Transferrin	200.7mg/dL	200~360mg/dL
Stool OB	Positive	Negative
CMV PCR	7000copies/mL (↑)	<500 copies/mL
Aspergillus Ag	Negative	Negative
Parvovirus B19 IgM/IgG	(-/+)	(-/-)



EGD findings : chronic superficial gastritis



BM findings : decreased red cell precursors with markedly increased myeloid : erythroid ratio (7:1)



Echo findings : normal LV systolic/diastolic function (EF=62%) with normal LV wall thickness

Conflicts of Interest : None

Diagnosis

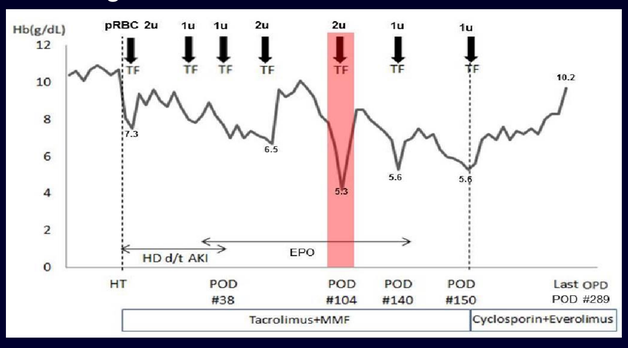
Pure red cell aplasia due to BM damage secondary to immunosuppressive agents

Management

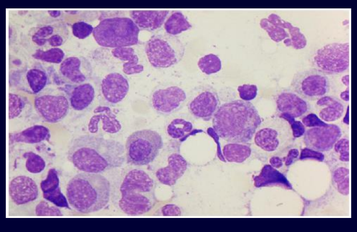
➔ Change immunosuppressive agents from tacrolimus to cyclosporin, from MMF to everolimus

➔ Hb level was elevated without transfusion after change of immunosuppressive agents

Hb changes after HT



Pure red cell aplasia



- **Normocytic normochromic anemia**
- **Severe reticulocytopenia**
- **Absence of erythroid precursors from the bone marrow**

Congenital PRCA	Solid tumors
Diamond-Blackfan anemia	Thymoma
Acquired PRCA	Gastric cancer
Primary	Breast cancer
Primary autoimmune PRCA (includes transient erythroblastopenia of childhood)	Biliary cancer
Primary myelodysplastic PRCA	Lung cancer
Secondary, associated with:	Thyroid cancer
Autoimmune/collagen vascular disorders	Renal cell carcinoma
Systemic lupus erythematosus	Carcinoma of unknown primary site
Rheumatoid arthritis	Infections
Inflammatory bowel disease	B19 parvovirus
Other immunologic mechanisms	Human immunodeficiency virus
ABO-incompatible stem cell transplantation	T-cell leukemia-lymphoma virus
Pyoderma gangrenosum	Infectious mononucleosis
Lymphoproliferative disorders	Viral hepatitis (hepatitis A, B, C, and E)
Chronic lymphocytic leukemia	Cytomegalovirus
LGL leukemia	Bacterial infections
Hodgkin disease	Group C *Streptococcus*
Non-Hodgkin lymphomas	Tuberculosis
Angioimmunoblastic lymphadenopathy	Bacterial sepsis
Multiple myeloma	Drugs and toxins
Waldenstrom macroglobulinemia	rhEpo-induced Epo antibody-associated PRCA
Castleman disease	Other drugs
Other hematologic malignancies	Other disorders
Chronic myelogenous leukemia	Pregnancy
Chronic myelomonocytic leukemia	Riboflavin deficiency
Myelofibrosis with myeloid metaplasia	

Drugs causing PRCA

Agent	Multiple reports	Mechanism investigated
Alemtuzumab		
Allopurinol	✓	
Ampicillin		
Azathioprine	✓	✓
Carbamazepine	✓	
Cephalothin		
Cladribine		
Chlorpropamide	✓	
Chloroquine		
Clopidogrel		
Dapsone/pyrimethamine	✓	
Diphenylhydantoin	✓	✓
Recombinant Epo	✓	✓
Estrogens		
Fenoprofen	✓	
Fludarabine	✓	
Interferon-α	✓	
Isoniazid	✓	✓
Lamivudine	✓	
Leuprolide	✓	
Linezolid	✓	
Micafungin		
Mycophenolate mofetil	✓	
d-Penicillamine	✓	
Phenylbutazone		
Procainamide	✓	
Ribavirin	✓	
Rifampicin		✓
Sulfasalazine	✓	
Sulindac		
Tacrolimus	✓	
Trimethoprim/sulfamethoxazole	✓	
Valproic acid	✓	✓
Zidovudine	✓	

Robert T. Means Jr, Blood. 2016

Conclusion

1. ***Pure red cell aplasia*** **is one of the various causes in post-transplant anemia**
2. **Immunosuppressive agents should be considered as a culprit of drug-induced pure red cell aplasia.**