Case conference

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Discussion

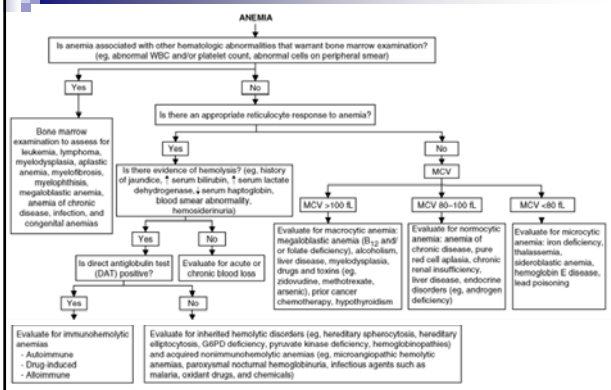
Anemia

The basic evaluation of a patient newly diagnosed with anemia

- **CBC**
- **Reticulocyte count** : reflects activity in the bone marrow and
- Mean cellular volume (MCV) is the most useful guide to the possible etiology of an anemia.
- ✓ The reticulocyte count, along with the MCV, can help classify an anemia quickly and helps provides an initial approach to the differential diagnosis
- **Peripheral blood smear**
- Two most common sources of blood loss: **gastrointestinal** and **uterine bleeding**

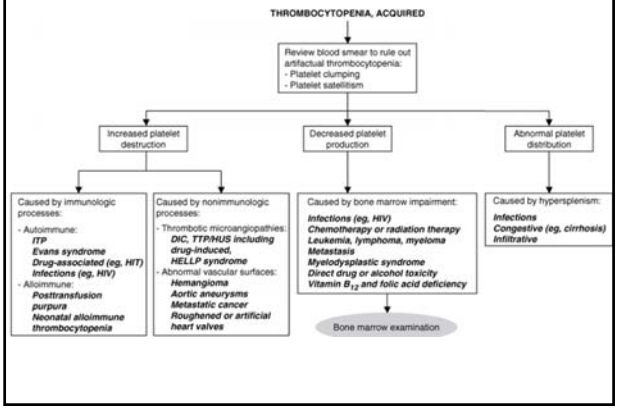
Table 218-3 Tests in the Evaluation of Anemia

Test	Interpretation	Clinical Correlation
MCV (mean corpuscular volume)	Measure of the average red blood cell size	Decreased MCV (microcytosis) is seen in chronic iron deficiency, thalassemia, anemia of chronic disease
		Increased MCV (macrocytosis) is seen in B_{12} or folate deficiency, alcohol abuse, liver disease, phenytoin, some HIV drugs
Reticulocyte count	These red blood cells of intermediate maturity are a marker of production by the bone marrow	Decreased reticulocyte count reflects impaired red blood cell production
		Increased counts are a marker of accelerated red cell production
Peripheral blood smear	Allows visualization of the red blood cell morphology	
	Allows evaluation for abnormal cell shapes	
	Allows examination of the white blood cells and platelets	



Type of Anemia	MCV (fL)	Common Causes	Common Laboratory Abnormalities	Other Clinical Findings
Microcytic, hypochromic	<80	Iron deficiency	Low reticulocyte count, low serum and bone marrow iron, high TIBC, high serum/plasma soluble transferrin receptor (sTfR).	Mucositis, blood loss.
		Thalassemias	Abnormal red cell morphology, normal serum iron levels, abnormal hemoglobin electrophoresis, high hemoglobin A_2 in β-thalassemia minor.	Asian, African, or Mediterranean descent.
Normocytic, normochromic	81–100	Acute blood loss	Fecal occult blood test positive if GI bleeding is the underlying cause.	Recent blood loss.
		Hemolysis	Haptoglobin low or absent, reticulocytosis, hyperbilirubinemia, high serum LDH, spherocytes or schistocytes on smear.	Hemoglobinuria, splenomegaly.
		Chronic disease[1]	Low serum iron, TIBC low or low normal, normal sTfR, normal or high bone marrow iron stores with rare or no sideroblasts.	Depends on cause, typically chronic inflammation.
Macrocytic, normochromic	>101[2]	Vitamin B_{12} deficiency	Hypersegmented PMNs, macro-ovalocytes, low serum vitamin B12 levels, high serum/urine MMA, achlorhydria.	Peripheral neuropathy, glossitis.
		Folate deficiency	Hypersegmented PMNs, macro-ovalocytes, low serum and red cell folate levels.	Alcoholism; malnutrition.
		Liver disease	MCV usually <120 fL; normal serum vitamin B_{12} and folate levels.	Signs of liver disease.
		Reticulocytosis	Marked (>15%) reticulocytosis.	Variable, including acute hemorrhage or hemolysis.

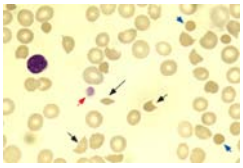
Thrombocytopenia



Anemia& Thrombocytopenia

Anemia & thrombocytopenia

- Microangiopathic hemolytic anemia (MAHA)
- Autoimmune hemolytic anemia (AIHA)



TTP&HUS

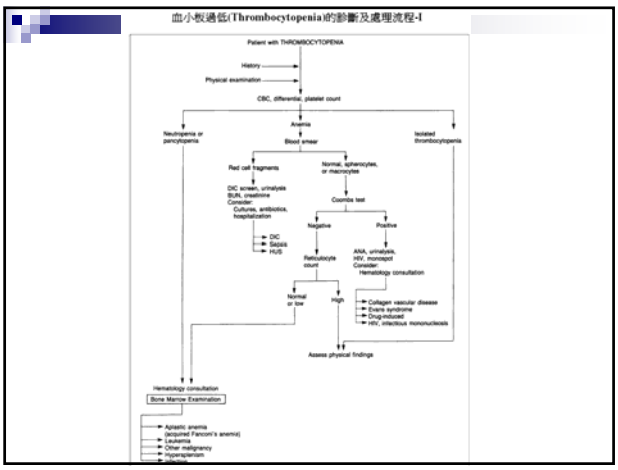
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- MAHA + thrombocytopenia→ Multiple organ involve

Complete blood count
Anemia (microangiopathic hemolytic anemia)
Thrombocytopenia (especially severe in TTP)
Increased reticulocyte percentage
White blood cell count normal to increased
White blood cell differential normal with no immature granulocytes
Peripheral blood smear
Polychromatophilic red cells (ie, reticulocytosis)
Fragmented red cells (schistocytes, helmet cells)
Nucleated red cells may be present, but are not numerous*
Coagulation and Immunohematologic studies
Normal PT
Normal aPTT
Fibrinogen concentration normal*
Fibrin degradation products not increased*
Direct Coombs' test negative
Other laboratory studies
Markedly increased serum lactate dehydrogenase (LDH)
Increased serum indirect bilirubin
Markedly reduced or absent serum haptoglobin
Increased serum creatinine (especially in HUS)

D/D DIC

Multiple organ failure

- TTP : Neurologic abnormalities >acute renal failure
- HUS : Acute renal failure>neurologic abnormalities
- TTP-HUS



Bone marrow failure

The differential diagnosis of pancytopenia without prominent splenomegaly

- Aplastic anemia
- Marrow replacement
- Overwhelming infection
- ….

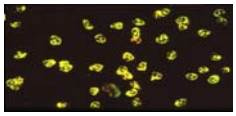
Pharmacology and toxicity of thionamides

Common side effects

- Both Methimazole(MMI) and (Propylthiouracil) PTU can cause pruritus, rash, urticaria, arthralgias, arthritis, fever, abnormal taste sensation, nausea, or vomiting in up to 13 percent of patients
- If one drug is not tolerated, the other drug can be substituted, but up to 50 percent of patients have cross-sensitivity

ANCA-positive vasculitis

- An antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis has been reported in association with PTU and MMT use
- Positive ANCA ≠vasculitis
- Mimic diagnosis



Diagnosis for vasculitis

- Positive ANA
- Elevated CRP , ESR
- Leukocytosis with eosinophilia
- Increased rheumatoid factor

Hepatotoxicity

- Hepatotoxicity is a rare complication of thionamide therapy. Serum aminotransferase concentrations increase transiently in up to one-third of patients taking PTU; this abnormality may be associated with focal hepatic necrosis on liver biopsy

Cholestatic jaundice

- MMI has been associated with liver disease, it is typically due to cholestatic dysfunction not hepatocellular inflammation

Cholestatic jaundice

- A 43-year-old woman had severe jaundice and itching 1 month after receiving methimazole (10 mg tid) and propranolol (20 mg tid) for treatment of hyperthyroidism.
- When seen at the emergency department 2 weeks later, she still had severe icterus, pruritus, and hyperbilirubinemia, formed mainly of the conjugated fraction.
- Methimazole-induced cholestasis was diagnosed, and propranolol therapy was resumed. Over the following 9 days, the symptoms improved and plasma bilirubin levels were normal after 12 weeks without methimazole.

South Med J 2004 Feb;97(2):178-82.

Agranulocytosis

- Agranulocytosis is a rare but serious complication of thionamide therapy, with a prevalence of 0.2 to 0.5 percent, and usually occurs within the first two months of treatment
- Risk factor : Elderly , high dosage
- Recovery from agranulocytosis takes a few days after cease drug
- May need G-CSF , antibiotics if infection

Aplastic anemia

- Usually sudden onset of symptoms after a relative short time of exposure to the drugs
- All have concomitant agranulocytosis
- Most have a rapid recovery following discontinuation of the drug and supportive treatment

Antithyroid Drug-Induced Aplastic Anemia

THYROID
Volume18, Number 10,2008

TABLE 1. DIFFERENCES BETWEEN THE VARIOUS ANTITHYROID DRUGS THAT CAUSE APLASTIC ANEMIA AND AGRANULOCYTOSIS

	Methimazole		*Carbimazole*		*Propylthiouracil*	
	Aplastic anemia	*Agranulocytosis*	*Aplastic anemia*	*Agranulocytosis*	*Aplastic anemia*	*Agranulocytosis*
Published cases	32	>250[c]	2	>60[c]	2	>22[c]
Age related[a]	no	yes (elderly)	no	yes (elderly)	—	yes (elderly)
Dose related	yes	yes	yes	yes	—	no
Mortality[b]	<10%	<2%[d]	<50%	<5%[d]	—	<1%[d]

[a]Aplastic anemia and agranulocytosis occur more frequently in female patients (Ref. 6).
[b]Deaths occur more frequently in older patients (>65years) (Ref. 6).
[c]In addition, more than 30 patients with MMI, 90 with CBM, and 20 with PTU induced agranulocytosis have been reported in Yellow Card Scheme data and the studies of the International Aplastic Anemia and Agranulocytosis Groups (Ref. 6, 7). Although slightly higher rates of agranulocytosis are observed with PTU compared to MMI, MMI accounts for 75% of the cases of agranulocytosis, most probably because is more frequently prescribed.
[d]Deaths with various rates (2–20%) have been reported in published cases (6, 7, 37, 38), but a mortality rate of 0% was found in the largest study that enrolled 109 patients (17).

Patient

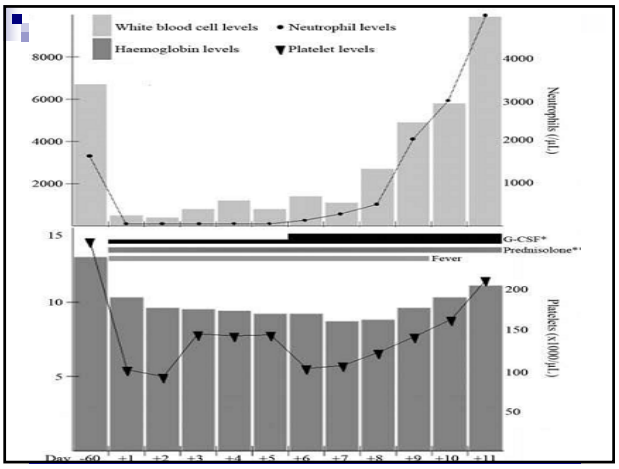
- A 28-year-old woman presented with a 2-week history of fine tremor , tachycardia , muscular weakness,and periorbital edema.The diagnosis of Graves'disease was made and she was started on CBM 30mg/d and propranolol; forty-five days later she became clinically and biochemically euthyroid and the dose of CBM was reduced

TABLE 2. THYROID FUNCTION DURING THE COURSE OF THE DISEASE IN BOTH PATIENTS WITH AA

Case	*Thyroid function tests*	*Diagnosis*[a]	*Following antithyroid drug administration*	*Current admission*	*Thyroidectomy*
1	TSH (mIU/L)(N.R: 0.4-4.9)	0.01	0.1	0.01	0.03
	FT_4 (ng/dL)(N.R: 7.5-19.4)	28.1	10	22	20.2
	FT_3 (pmol/L)(N.R: 3.4-8.5)	18.9	8.5	6.1	5.7

Patient

- Two weeks later she developed pyrexia (temperature 40'C) , headache photophobia,and cervical rigidity
- A complete blood count (CBC) revealed agranulocytotosis,anemia (reticulocyte count 0.02%),and thrombocytopenia
- CT and a lumbar puncture were normal
- Thyroid function tests revealed mild hyperthyroidism
- A bone marrow aspirate showed severe marrow hypoplasia with very little hemopoeitic cells,increased fat spaces , deposition of hemosidirin and markedly reduce erythrocytes,granulocytes,and megakaryocytes



- CBM was discontinued
- Broad-spectrum antibiotics , acyclovir, voriconazole and were administered
- Lugol iodine solution prednisolone and propranolol were also given to control the hyperthyroid state
- Recover on 10th admission day

Monitoring CBC ?

- Controversy exists as to the value of monitoring white blood cell counts. Most clinicians in the United States do not recommend periodic monitoring.
- Patients taking a thionamide to have a white cell count with differential at the earliest sign of a sore throat or other infection, and to discontinue the drug until the result is available.