Anemia (2): 4 MS/18/02/2019

Case 2

65 yr old male had gradual onset of “odd” behavior with psychotic symptoms, irritability and parasthesia in hands and feet

He was noticed to have imbalanced gait. Examination showed loss of vibration

and proprioception in lower limbs

Laboratory tests

Hb **5** g/dl, MCV **112**,

Retics (corrected)0.**009**

WBC 3.3k, Platelets 112k

LDH 1900. Serum B12 30pg/ml.

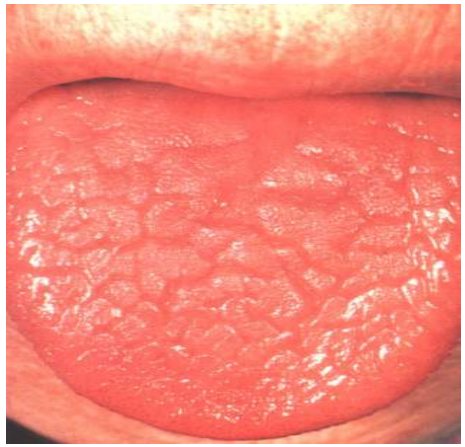
IF Ab +PCA+

Achlorhydria+

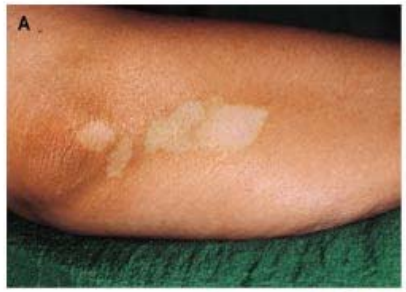
Gastric Bx atrophic gastritis.

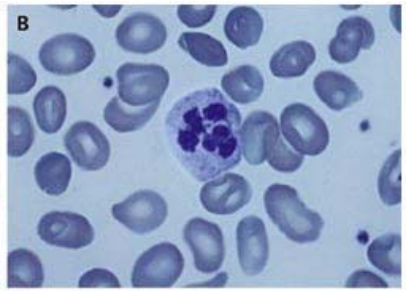
Physical And Lab

Red Beefy Tongue

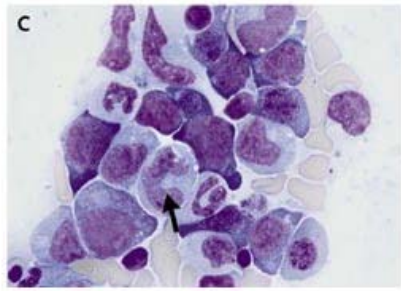


Vitiligo

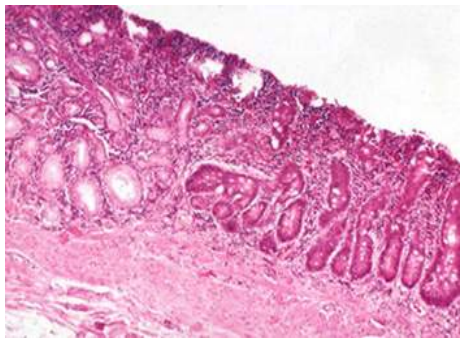




Macro-ovalocytes.hyperseg



BM: Megaloblasts



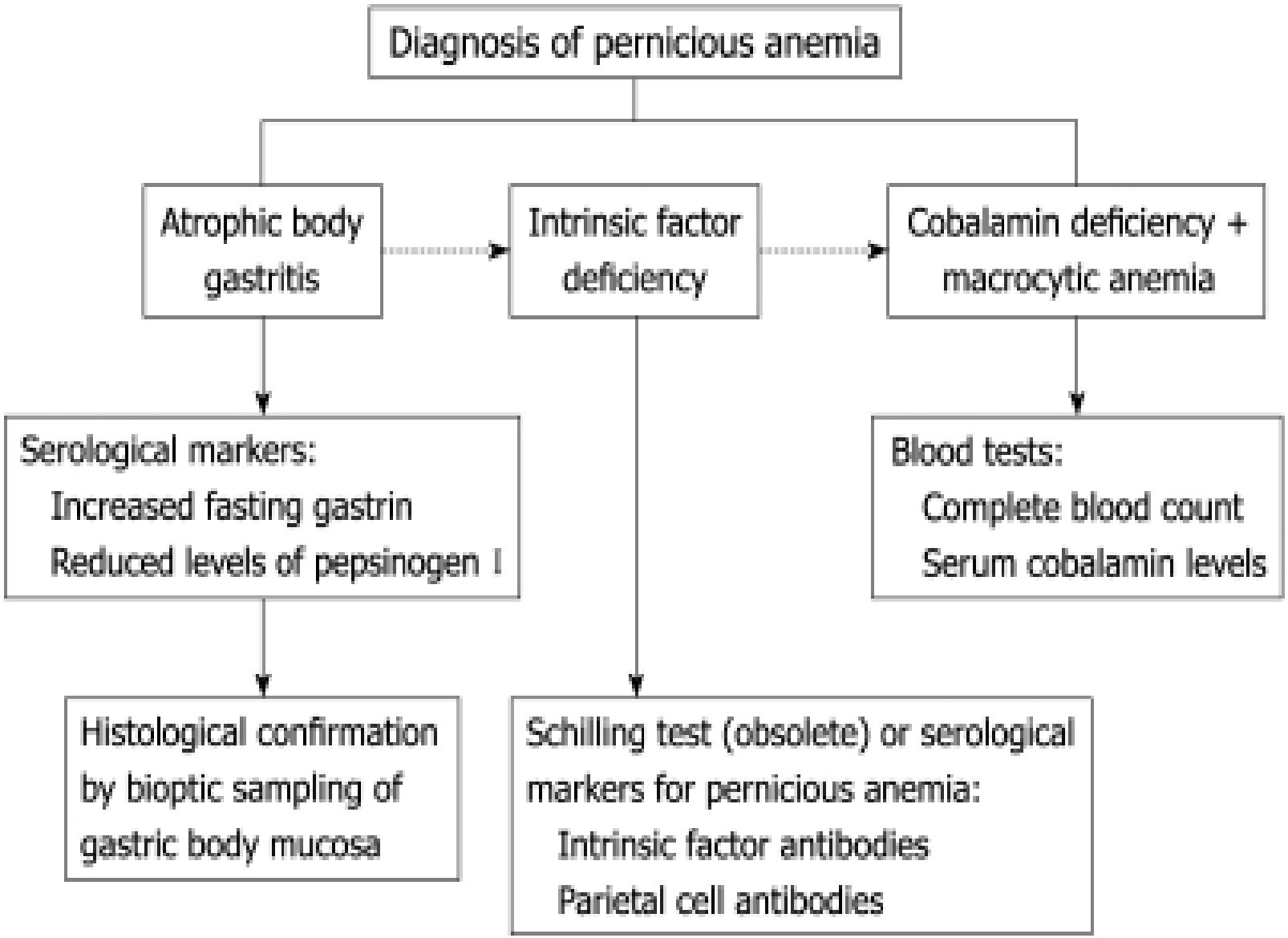
Oxyntic G. mucosa atrophy

Pathogensis of Pernicious Anemia (PA)

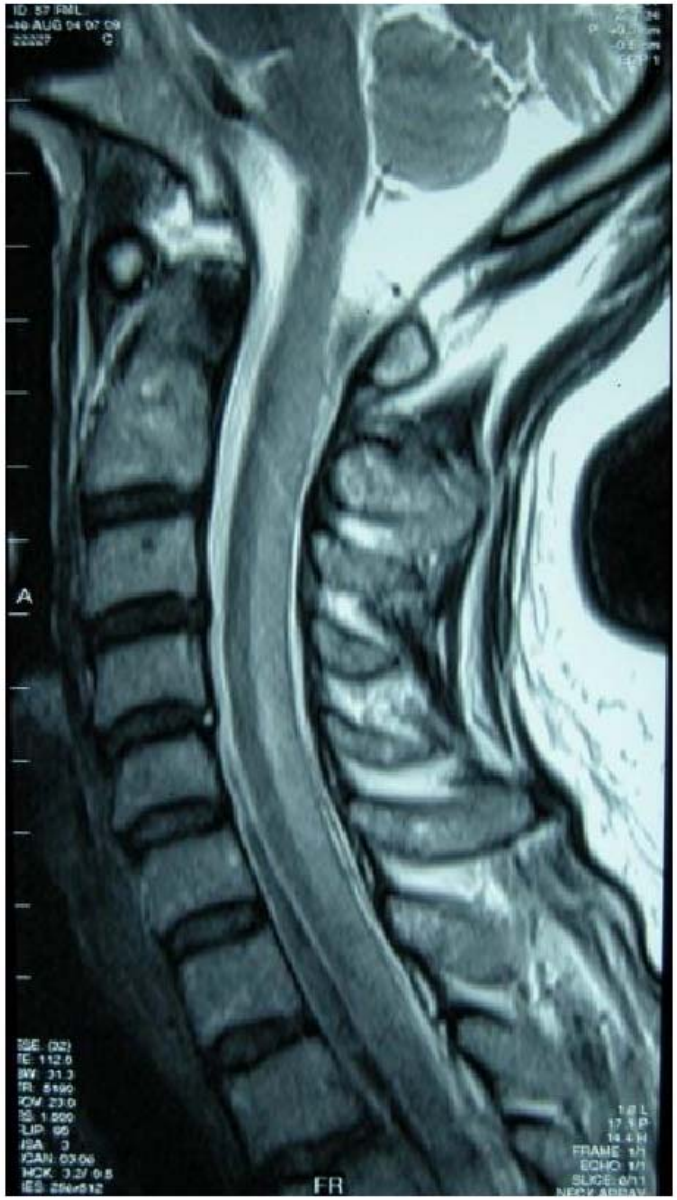
1-PA is the end-stage of Atrophic Body Gastritis (ABG) causing oxyntic gastric mucosa damage: achlorhydria.

2-It is considered an autoimmune disease (AID).

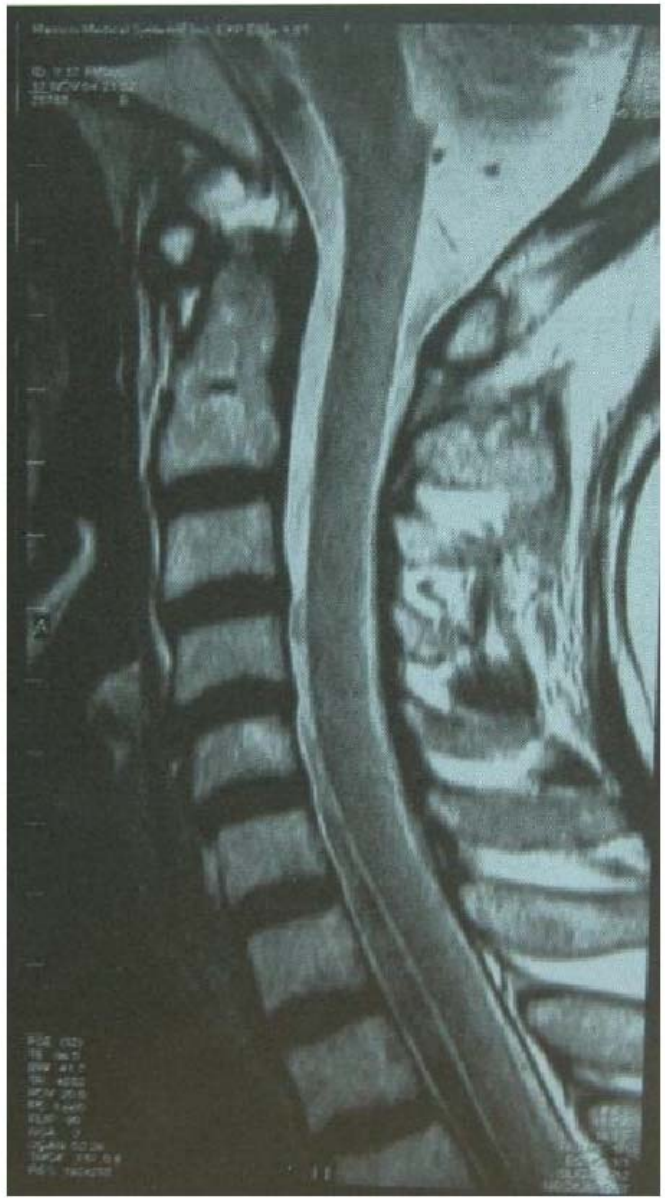
3-AID theory is based on the presence of parietal cell and/or intrinsic factor autoantibodies
Frequent association with other autoimmune disorders: autoimmune thyroid disease (ATD), type 1 diabetes, and vitiligo


Diagnosis of pernicious anemia
Atrophic body gastritis
Intrinsic factor deficiency
Cobalamin deficiency + macrocytic anemia
Serological markers:
Increased fasting gastrin
Reduced levels of pepsinogen I
Blood tests:
Complete blood count
Serum cobalamin levels
Histological confirmation by bioptic sampling of gastric body mucosa
Schilling test (obsolete) or serological markers for pernicious anemia:
Intrinsic factor antibodies
Parietal cell antibodies

A-Before therapy



B-Post-therapy



A-Hyperintense in cervical region

B-corrected

Subacute Combined Degeneration of Spinal Cord

Other causes of cobalamin deficiency

Gastric causes of impaired absorption:
Gastrectomy/ gastric sleeve operations

Corpus-predominant *H pylori* gastritis

Long-term proton pump inhibitor therapy

Ileal disease or resection

Blind loop syndrome

Fish tapeworm

Severe pancreatic insufficiency

Decreased intake due to vegetarianism

Other causes of macrocytic anemia

Folate deficiency

Drugs (e.g. methotrexate, azathioprine, 6-mercaptopurine)

erythropoiesis: hemolysis, response to hemorrhage

Liver disease (alcoholic, cirrhosis, poor dietary intake)

Hypoplastic anemia, myelodysplastic syndrome

Chronic obstructive pulmonary disease

Case 2 : Treatment & Monitoring

No Blood Transfusion

Vit B12 IM injections daily 7-10 days. Then monthly lifelong.

Careful monitoring of response

Careful monitoring for gastric Ca

Careful monitoring for thyroid function & DM

Response to Treatment

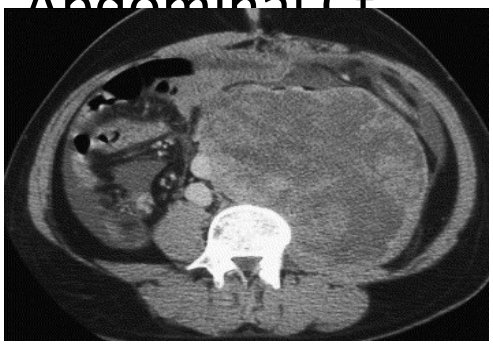
Reticulocytosis in 3-4days, peak 5-10 days
Rise in Hgb concentration within 10 days and normalization in 8-10 weeks as well as correction of MCV.
Fall of serum LDH levels within 2 days
Hypersegmented PMN disappear in 10-14 days
Watch closely for severe hypokalemia during early response.
Megaloblastic changes disappear within 2 days

Case 2 B

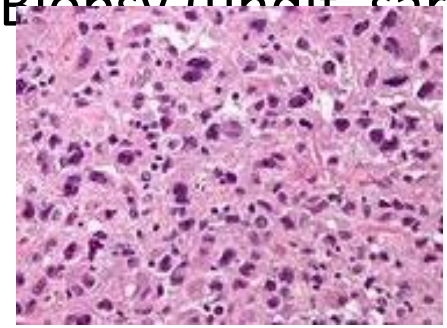
65 yr old male had “anemia syndrome” over the last 6 weeks. He noticed abdominal swelling and weight loss. He had mild fever and night sweats for 2 weeks. No neurological symptoms or signs.

Hb 9, MCV 106, WBC 5.3, Plt 142, Retics (corrected)0.1%. Serum B12 normal. LDH 1100. serum folate was 0.2

Abdominal Ct



Biopsy (undif. sarcoma)



Causes of Folic acid deficiency

1. Inadequate intake

- diet lacking fresh, uncook food; chronic alcoholism, total parenteral nutrition,

2. Malabsorption

- small bowel disease (sprue, celiac disease,)
- alcoholism

3. Increased requirements:

- pregnancy and lactation
- infancy
- chronic hemolysis
- **malignancy**
- hemodialysis

4. Defective utilisation

Drugs:folate antagonists(methotrexate, trimethoprim, triamteren), purine analogs (azathioprine), primidine analogs (zidovudine), RNA reductase inhibitor (hydroxyurea), miscellaneous (phenytoin, N_2)

Case 2 B:
Treatment and follow-up

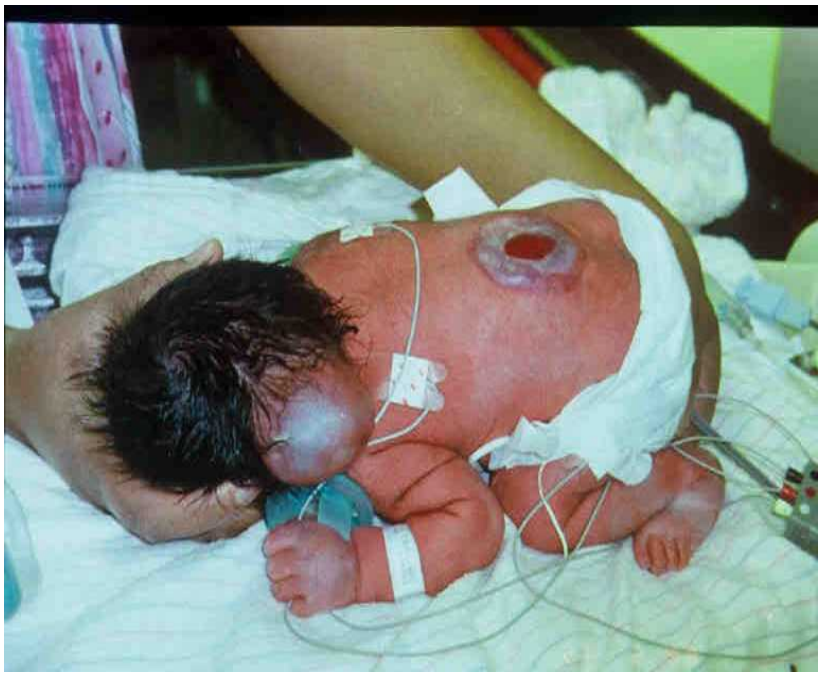
Treat the original Cause

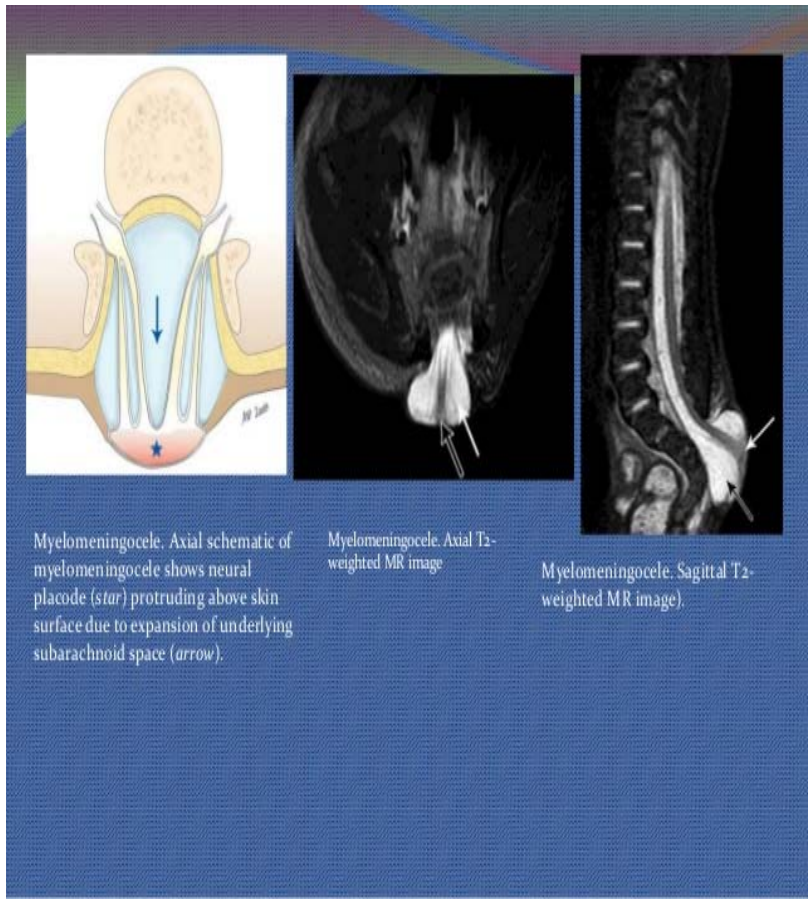
Oral administration of folic 5 mg x2daily, for 3 months, and maintenance therapy if it is necessary.

Retics after 5-7 days.

Correction of anaemia after 2 months therapy.

Folic acid has role in neural tube closure in foetus, a pregnant woman should have enough folate to protect her foetus from having neural tube defects





Myelomeningocele. Axial schematic of myelomeningocele shows neural placode (*star*) protruding above skin surface due to expansion of underlying subarachnoid space (*arrow*).

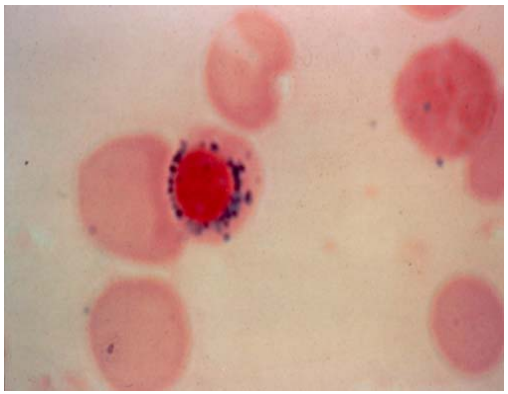
Myelomeningocele. Axial T2-weighted MR image

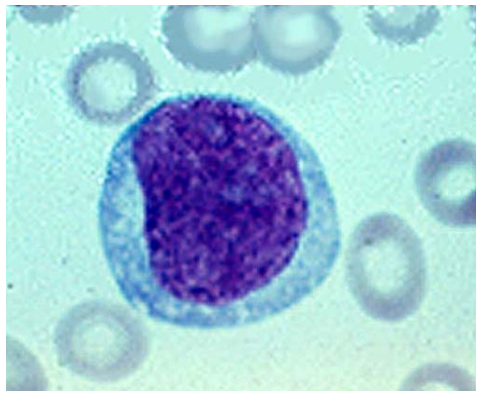
Myelomeningocele. Sagittal T2-weighted MR image).

Case 2 C

48 yr old lady presented with “anemia syndrome” for 3 months. She was found to have splenomegaly. Hb 8g, MCV 107fl, WBC 3.6, plt 95k, retics 0.6%.LDH350

BM: ringed sideroblasts, blasts 8%. Cytogenetics by FISH 11 q del.





Diagnosis: MDS: RARS/RAEB type I with ring sideroblasts

What are MDS?

- MDS: a spectrum of heterogeneous malignant hematopoietic stem cell disorders characterized by ineffective and dysplastic changes in BM with
  - ineffective haemopoiesis- dysmorphic cells in blood
  - Variable cytopenia- frequent progression to aml
- MDS may occur

  a-de novo: primary MDS b-as a result of haemopoietic stem cell injury: secondary or treatment-related MDS
- MDS is associated with significant morbidity and mortality due to
  - cytopenias
  - impaired quality of life
  - risk of transformation to AML

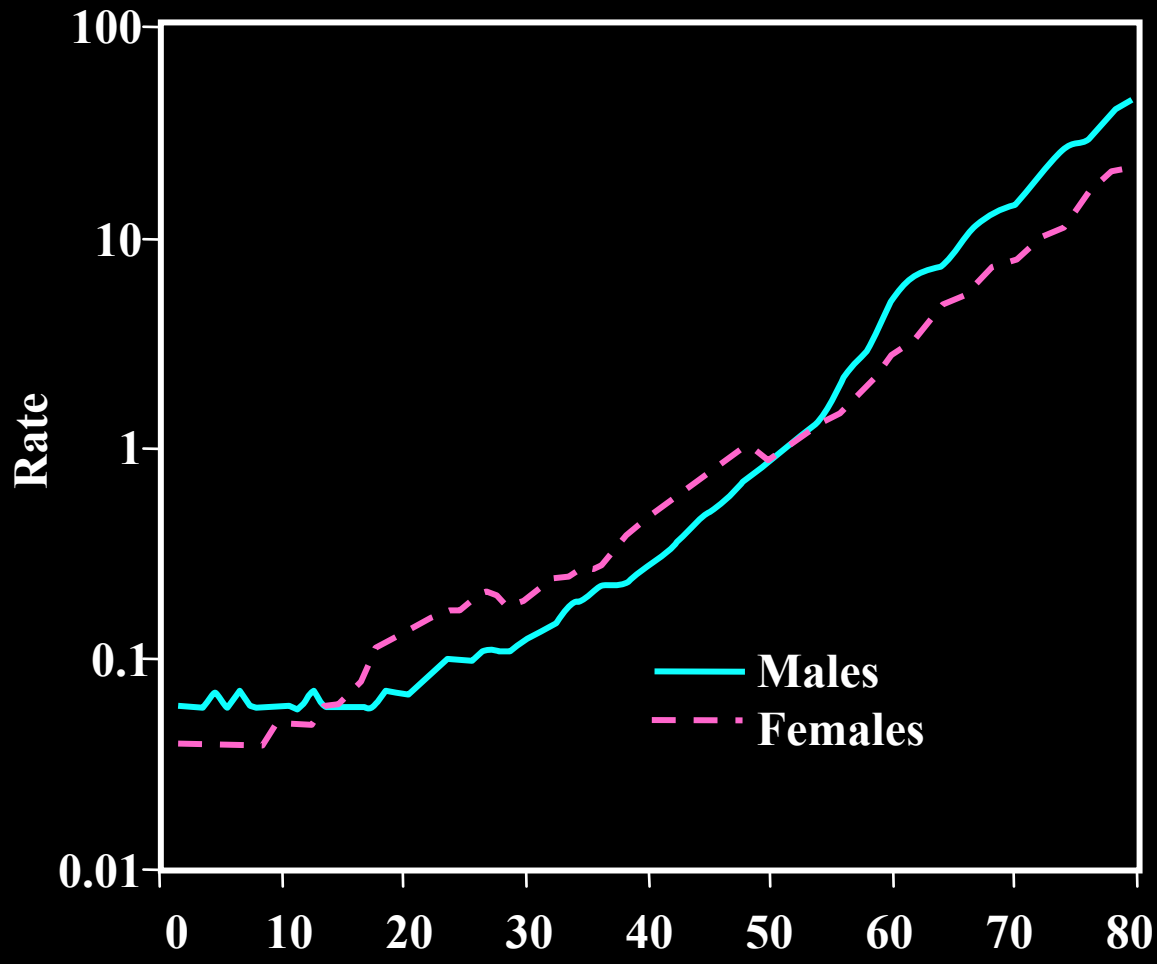
Epidemiology of MDS

- Epidemiology of MDS
  - common bone marrow disorder
  - the overall incidence is approximately 5 per 100,000 in the general population
  - peak incidence occurs at 60–90 years of age

    > 20 per 100,000 at 70 years of age
- Typical MDS patient
  - elderly
  - slight male preponderance
  - approximately 50% have a cytogenetic abnormality

Age-related Incidence of MDS

Leukaemia Research Fund [1984-1993]



McNally RJQ et al. *Hematological Oncology* 1997. 15:173-189,
Cartwright RA,et al. Leukaemia Research Fund, 1997. http://www.lrf.org.uk
Reprinted with Permission of Leukemia Research Fund

Pathogenesis

Poorly understood
Clonal process, thought to arise from single hematopoietic progenitor cell that acquired multiple mutations
Global hypomethylation with concomitant hypermethylation of gene-promoter regions.
Mutation in genes that encode enzymes, such as TET2, IDH1, IDH2
As role for immunosuppressive agents, suggest immune system implicated in myelosuppression and/or marrow hypocellularity

Clinical features in MDS

- Anaemia
  - > 80% of patients with MDS are anaemic at diagnosis
  - Granulocytopenia
  - 50–70% of patients
  - predisposition for infections
- Thrombocytopenia in 30% of patients
- In MDS
  - chronically low Hb levels associated with cardiac remodelling and increased incidence of heart failure

Diagnosing MDS

Cytopenia(s) → suspect MDS

Recommended evaluations

- History and physical examination
- Complete blood, platelets, differential, and reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics

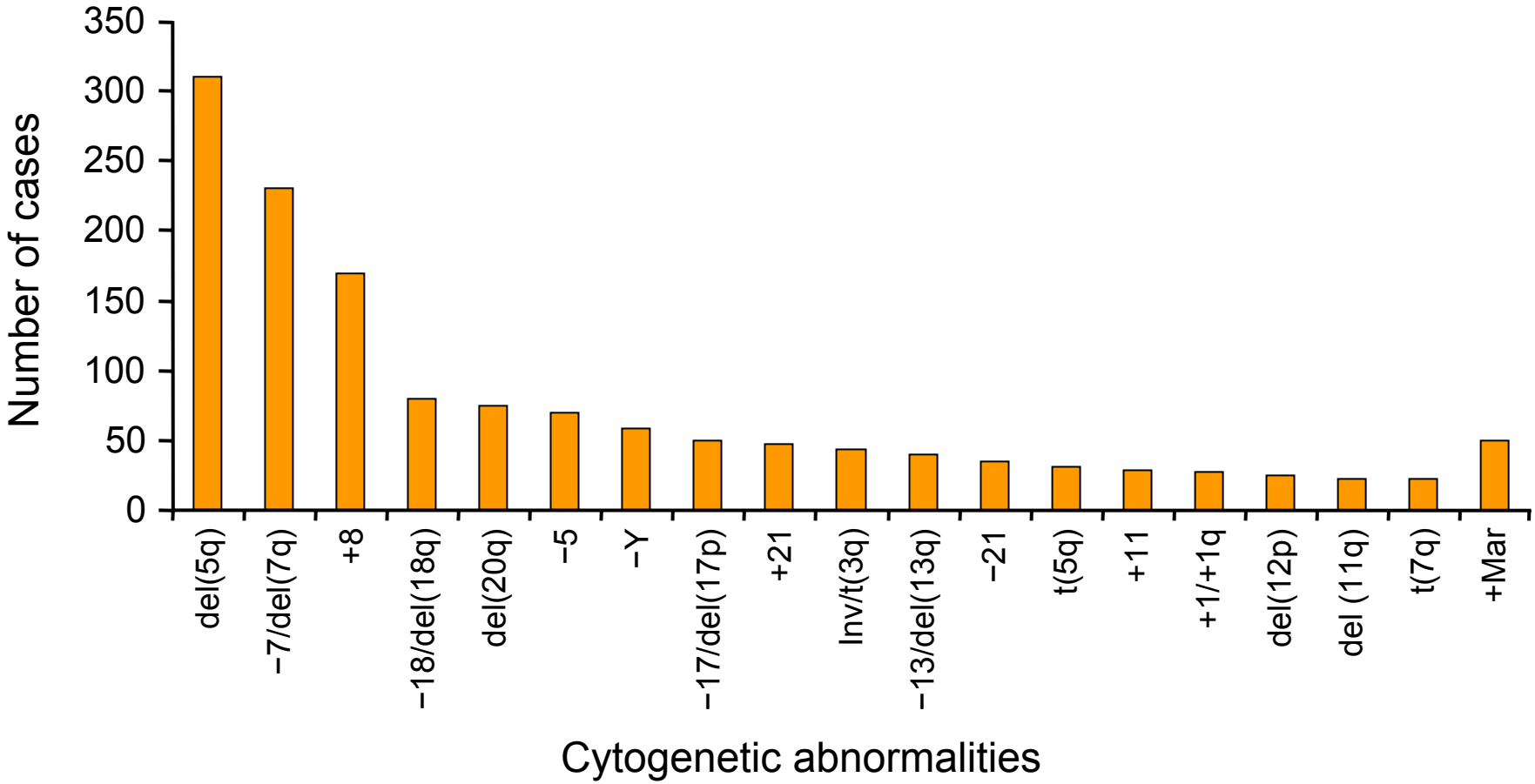
- Serum erythropoietin (prior to RBC transfusion)
- RBC folate and serum vitamin B_{12}
- Serum ferritin
- Documentation of transfusion history

Diagnosis of MDS based on morphologic and clinical criteria

Subtypes of MDS: WHO classification

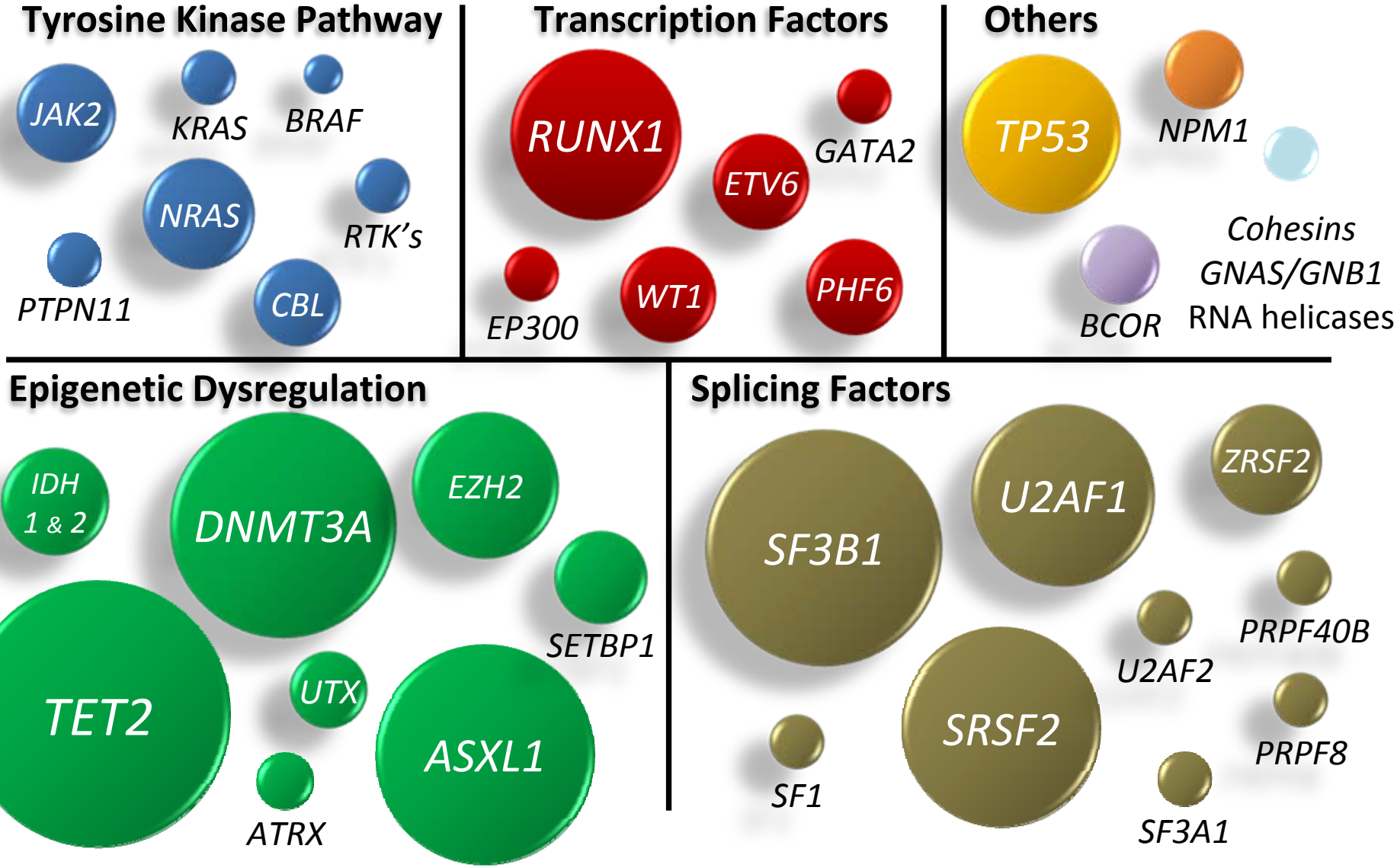
Disease	Blood findings	Bone marrow findings
Refractory anaemia (RA)	Anaemia No or rare blasts < 1 × 10^9/L monocytes	Erythroid dysplasia only < 10% grans or megas dysplastic < 5% blasts, < 15% ringed sideroblasts
Refractory anaemia with ringed sideroblasts (RARS)	Anaemia No blasts	Erythroid dysplasia only < 10% grans or megas dysplastic ≥ 15% ringed sideroblasts, < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods, < 1 × 10^9/L monocytes	Dysplasia in ≥ 10% of cells in two or more myeloid cell lines < 5% blasts in marrow, no Auer rods, < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods, < 1 × 10^9/L monocytes	Dysplasia in ≥ 10% of cells in two or more myeloid cell lines ≥ 15% ringed sideroblasts, < 5% blasts, no Auer rods
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenias < 5% blasts No Auer rods, < 1 × 10^9/L monocytes	Unilineage or multilineage dysplasia 5–9% blasts, no Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenias 5–19% blasts Auer rods ±, < 1 × 10^9/L monocytes	Unilineage or multilineage dysplasia 10–19% blasts, Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts, no Auer rods	Unilineage gran or mega dysplasia < 5% blasts, no Auer rods
MDS associated with isolated del(5q)	Anaemia < 5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobulated nuclei < 5% blasts, no Auer rods, isolated del(5q)

Frequencies of the most common cytogenetic anomalies in patients with MDS

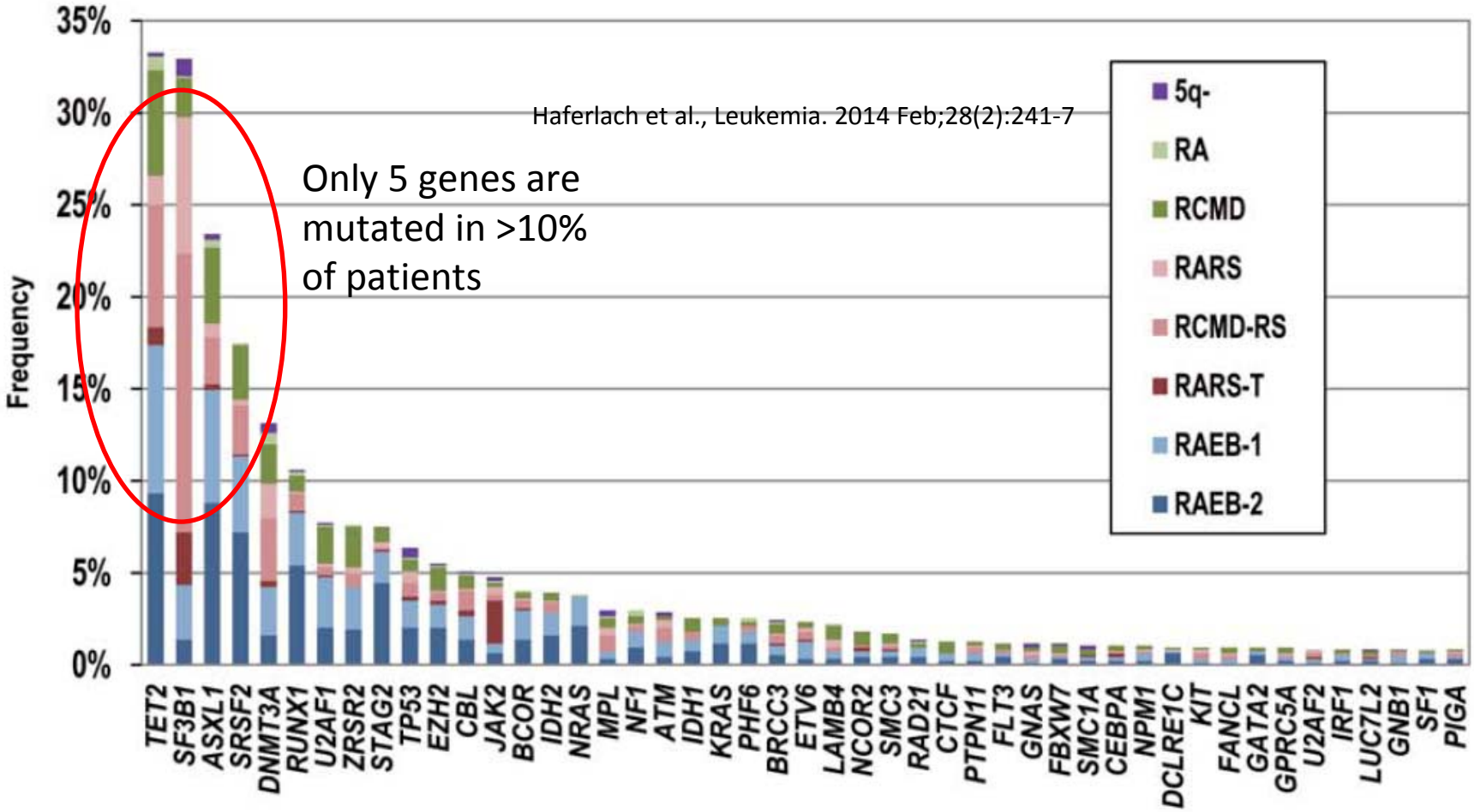


Haase D, et al. Blood. 2007;110:4385-95.

Point Mutations in MDS



Many mutations are very rare



WHO classification-based Prognostic Scoring System (WPSS)

Variable	0	1	2	3
WHO category	RA, RARS, isolation 5q−	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	–
Transfusion requirement	No	Regular	–	–

*Karyotype: **good**: normal, -Y, del(5q), del(20q); **poor**: complex (≥ 3 abnormalities), chr 7 anomalies; and intermediate: other abnormalities.

Score	WPSS subgroup	Median survival (months) Italian cohort	Median survival (months) German cohort
0	Very low	103	141
1	Low	72	66
2	Intermediate	40	48
3–4	High	21	26
5–6	Very high	12	9

Malcovati L, et al. J Clin Oncol. 2007;25:3503-10.

Case 2 C

WPSS

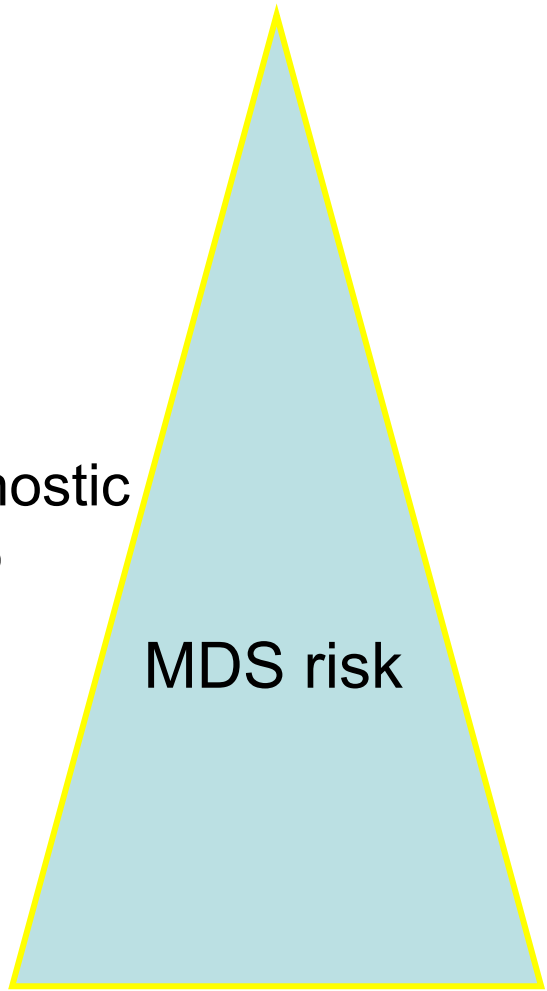
WHO category =2

Cytogenetics intermed. = 1

Bld Trx = 0

Total score 3. ms 21-26 months

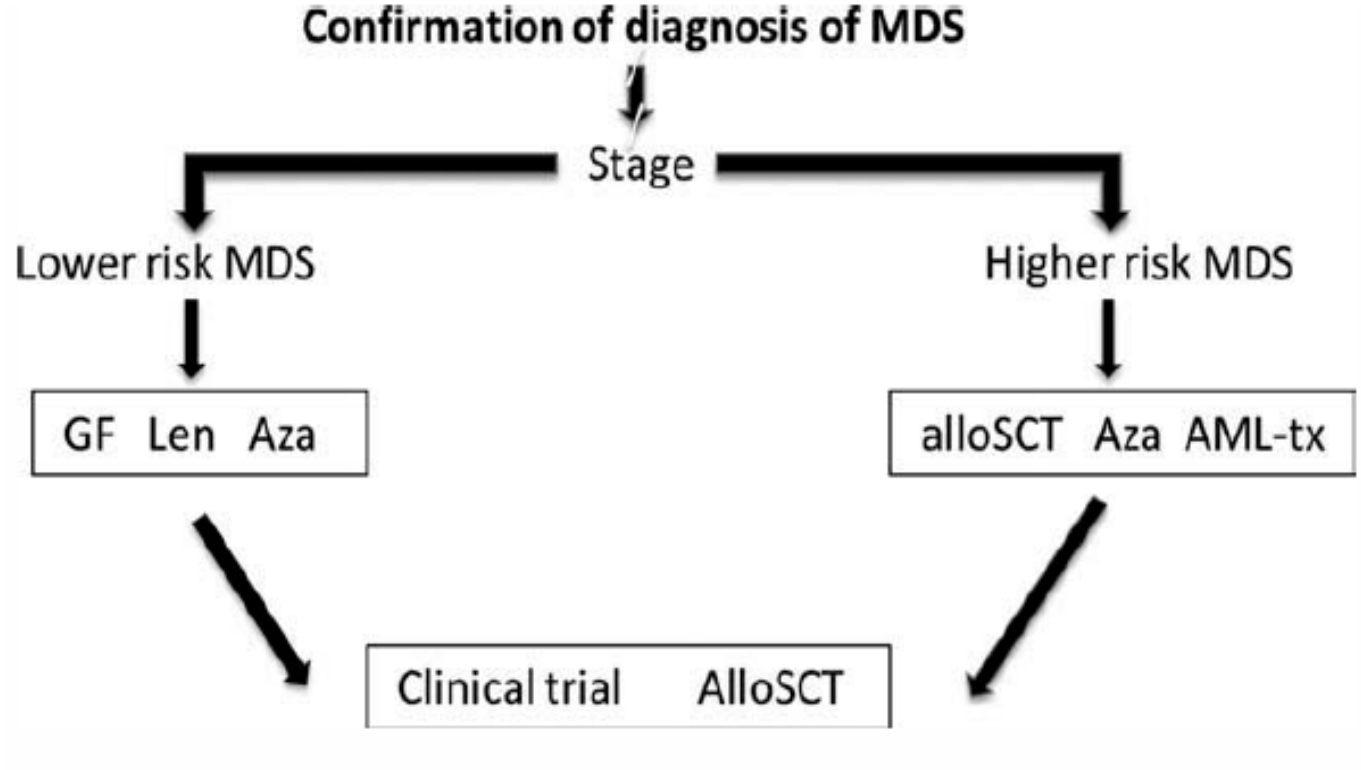
MDS: therapeutic options



- “Best supportive care”, including iron chelation
- Haemopoietic growth factors
- Immunosuppressive treatment
- Differentation induction
- Immunomodulatory drugs
- Arsenic trioxide
- Low-dose chemotherapy
- Epigenetic treatment
- Intensive chemotherapy
- Allogeneic SCT

SCT = stem cell transplantation.

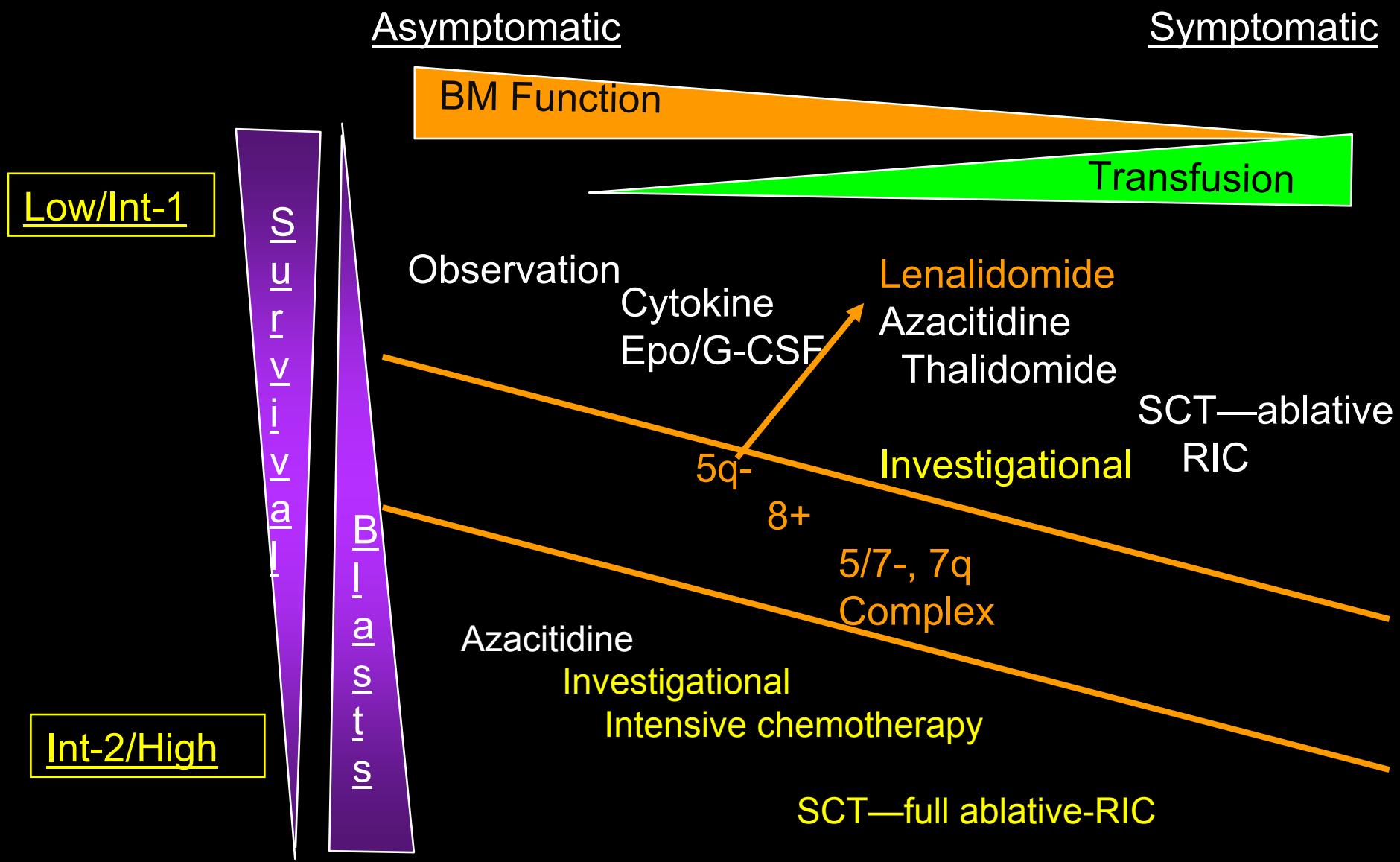
proposed general treatment algorithm



Treatments can be complicated by advanced age, comorbidities, chronicity of the disease.

Garcia-Manero, G. Am J Hematol. 2012.

Treatment Algorithm for Patients With MDS



RIC = reduced intensity conditioning.
From Silverman. In: Holland et al, eds. *Cancer Medicine*. 7th ed. BC Decker; 2006, .