

Bone Marrow Failure in Adults: Distinguishing Inherited from Acquired Causes

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Causes and Pathophysiology of Aplastic Anemia

Causes	Cytotoxic drugs Radiation Benzene	Idiopathic	Inherited bone marrow failure syndromes (IBMFS)
Pathophysiology	Direct damage to BM -iatrogenic, dose dependent, spontaneous recovery is expected	Immune destruction -Cytotoxic T cells induce apoptosis, acquired somatic mutations in STAT3 signaling pathway produced activated T cell, decreased Treg	Germline mutations -manifested in childhood -physical anomalies -multiple organ involvement -family history -predisposition to HM and solid malignancies

Pathophysiological mechanisms of acquired aplastic anemia

Immune destruction

1. Idiopathic aplastic anemia
2. Autoimmune diseases: SLE, thymoma

Direct injury

1. Drugs: cytotoxic drugs, chemotherapeutics, antiepileptics, antipsychotics, antibiotics
2. Radiation
3. Toxins: benzene, alcohol
4. Infection
 - 4.1 Sepsis
 - 4.2 Viral: hepatitis A, B, C, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), Human Herpesvirus 6 (HHV-6), Parvovirus B19

Why to Differentiate AA from IBMFS

- Signs, symptoms, and family history of patients with IBMFS are **absent in up to 40% of cases**
- For AA, IBMFS accounts for
 - 25% of pediatric patients**
 - 5-15% of adults age ≤ 40 years**
- Data is lacking in patients > 40 years of age without syndromic features

Why to Differentiate AA from IBMFS

- Patients with **IBMFS do not respond with IST**, leading to increased cytopenia-related complications
- Potential for **severe systemic toxicity** alters selection of the BMT preparative regimen
- Increase risk of **cancer post BMT**
- Testing of **at-risk relatives** who may be a donor for BMT

Inherited Bone Marrow Failure Syndromes (IBMFS)

Classical IBMFS

- Fanconi anemia (FA)
- Dyskeratosis congenita (DC)
- Shwachman Diamond syndrome (SDS)
- Diamond Blackfan anemia (DBA)

Non-classical IBMFS

- GATA2 deficiency
- Familial platelet disorders
 - Congenital amegakaryocytic thrombocytopenia
 - Thrombocytopenia with absent radii
- MECOM-associated syndromes
- Diseases related to RUNX1, ETV6, and ANKRD26

Fanconi Anemia

Congenital syndrome	Characteristic features	Gene affected/ inheritance	Diagnostic lab
Fanconi anemia (FA) Defect in DNA repair	-short stature, missing or dysmorphic thumbs and radii, café-au-lait lesions, microcephaly, developmental delay, aplastic anemia -AYA predisposition to MDS/AML , SCC esp. head and neck, brain tumors and other solid tumors	-FA genes (23 genes) (FANCA to FANCY) -variants in FANCA, FANCC, FANCG accounting for > 80 % -AR (most), X-linked recessive	-chromosome breakage test (gold standard) -mutation testing



Chromosome Breakage Test in Blood or Skin Fibroblast

- Increased chromosomal breakage in response to DNA damaging agents such as mitomycin C (MMC) or diepoxybutane (DEB)



Negative



Positive

Revertant Hematopoietic Clonal Evolution



**FA has a relatively high rate of revertant mosaicism
in blood cells (15–25%).**

Dyskeratosis Congenita (DC) and Telomere Biology Disorders (TBD)

Telomere Structure

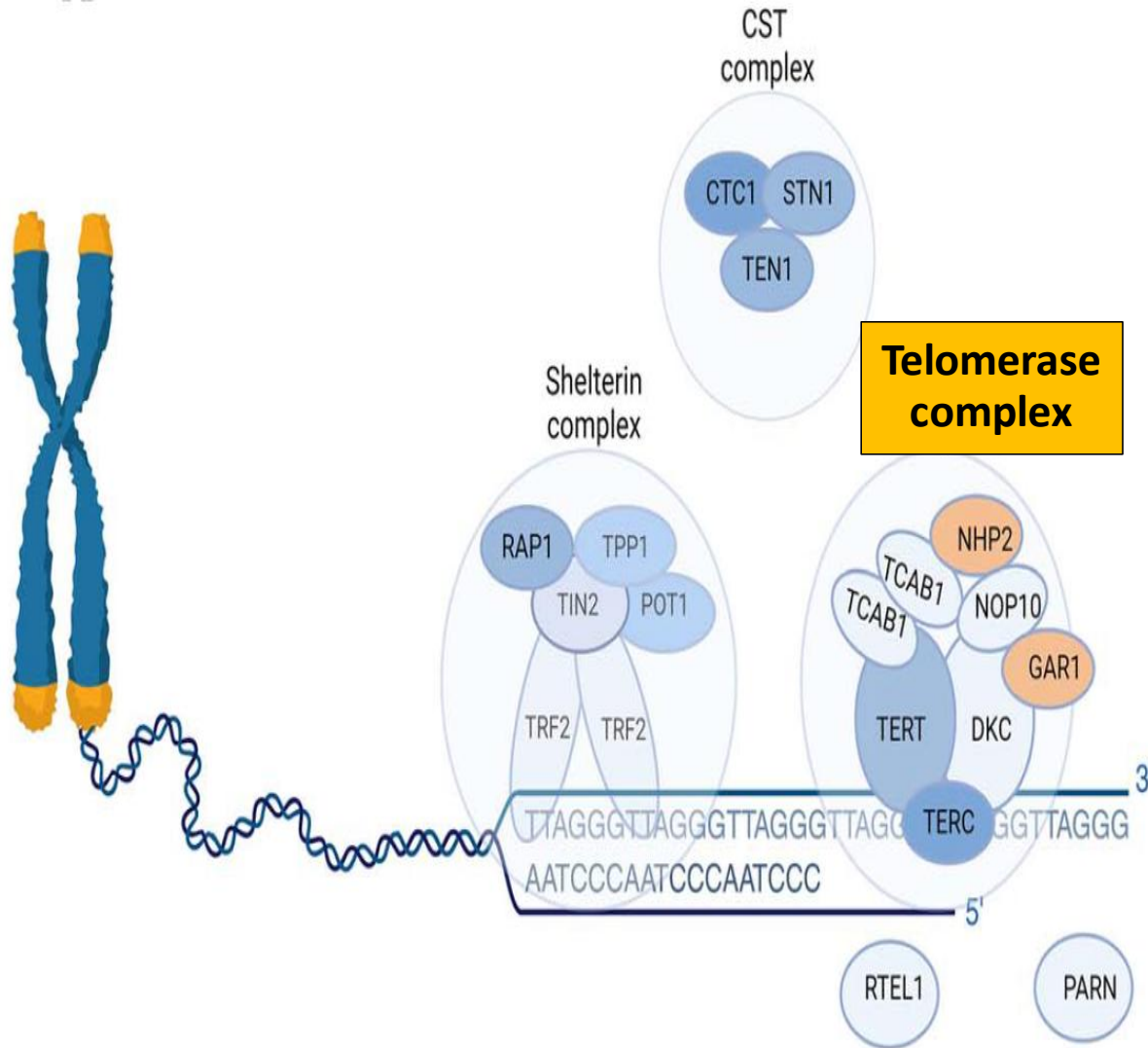


telomeres

telomeres

- **Telomeres** consist of $(TTAGGG)_n$ repeats and protein complex at the chromosome ends **essential for chromosomal stability**.
- Nucleotide **repeats shorten with each cell division** due to the inability of DNA polymerase to fully replicate the 3' ends of DNA.
- When telomeres **reach a critical length, cells undergo apoptosis** or enter senescence.

Telomere Structure



- Telomerase adds (TTTAGG) repeats to the end of the DNA after replication for maintaining telomere length in dividing cells e.g. stem cells, germ cells.
- Patients with **TBD** have very short telomeres for their age due to germline mutations in key telomere biology genes.

Congenital syndrome	Characteristic features	Gene affected/inheritance	Investigation
Dyskeratosis congenita (DC) Defect in telomere maintenance	-reticulated skin hyperpigmentation, nail dystrophy, mucosal Leukoplakia, aplastic anemia, lung fibrosis, liver fibrosis -AYA predisposition to MDS/AML, squamous cell cancers, and other solid	-DKC1 and other genes -X-linked recessive (most), AD and AR	-telomere length measurement in lymphocytes -mutation testing



Nail dysplasia



Lacy skin pigmentation

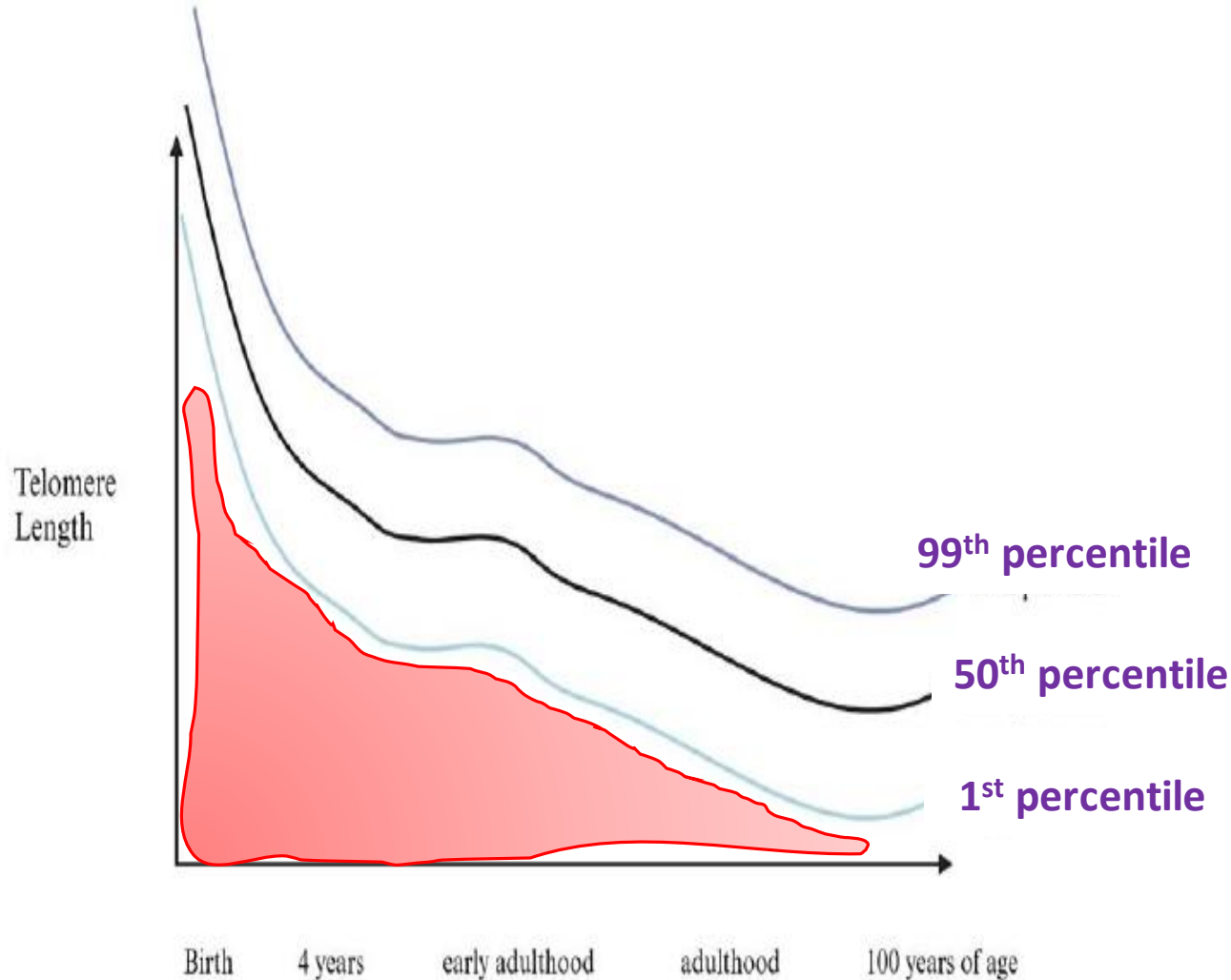


Oral leukoplakia



Flow Cytometry with Fluorescent in Situ Hybridization (Flow FISH) of Lymphocyte

Telomere length



- Flow FISH lymphocyte telomere lengths **< 1st percentile for age** are **highly sensitive (97%)** and **specific (91%)** for diagnosing patients with TBDs. 1st - 10th percentile can be seen esp. in patients older than age 40 years.
- Telomeres **< 1st percentile** rarely occur **in** patients with **other inherited BMF syndromes**.
- Reports showed patients with acquired AA with short telomeres but may not be **< 1st percentile**.

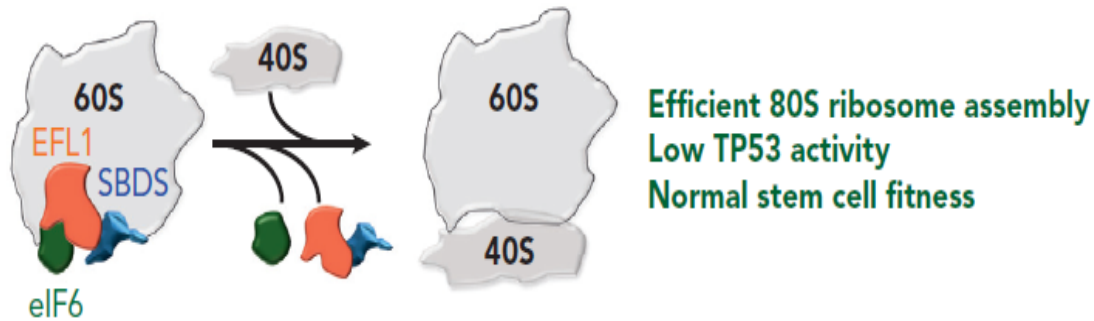


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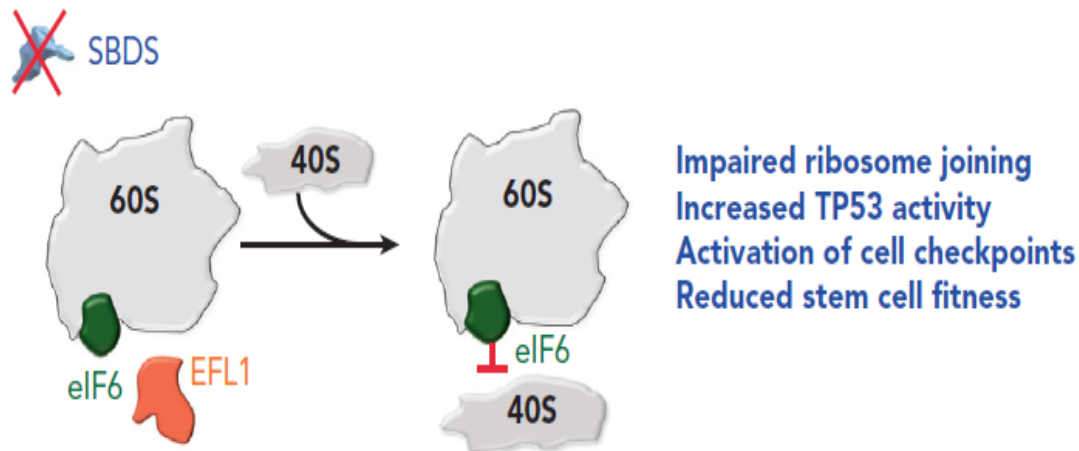
Shwachman-Diamond syndrome (SDS)

Ribosome Biogenesis and the Pathobiology of SDS

Normal ribosome subunit joining

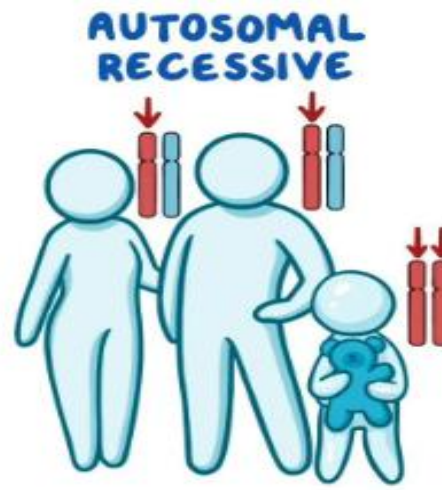
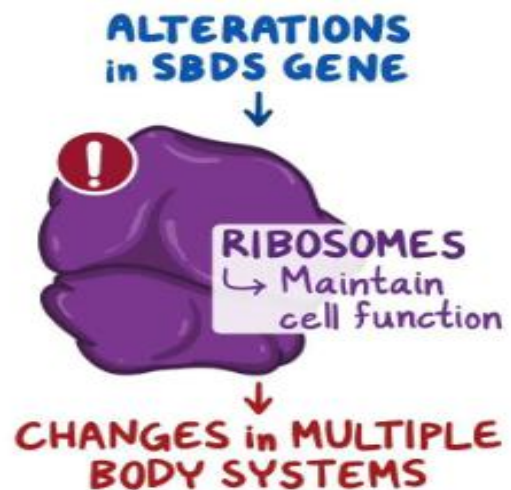
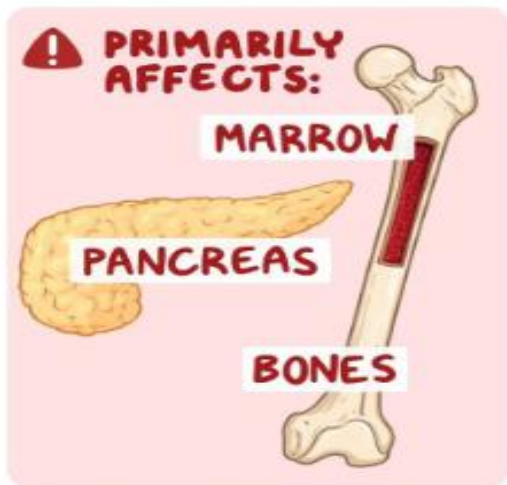


Shwachman-Diamond Syndrome



- Ribosomes = ribosomal RNAs (60S and 40S subunits) + ribosomal proteins, which perform translation of mRNA to proteins
- SBDS and EFL1 are required for joining of 60S and 40S subunits to form the translationally competent 80S ribosome.
- SBDS deficiency results in impaired ribosome subunit joining → impairment of translational capacity, reduced HSC fitness, and upregulation of TP53 activity

Congenital syndrome	Characteristic features	Gene affected/inheritance	Investigation
Shwachman-Diamond syndrome (SDS) Defect in ribosome biogenesis	-exocrine pancreatic insufficiency -> failure to thrive, steatorrhea, short stature, skeletal abnormalities, neutropenia (common), aplastic anemia (10-25%) -AYA predisposition to MDS/AML, no established risk of solid tumors	-SBDS ~ 90% -rare genes: EFL1, DNAJC21, and SRP54 -AR (most), AD	-age-adjusted pancreatic enzyme concentrations (trypsinogen, isoamylase) -mutation testing



Management for FA, DC, and SDS

- **Supportive treatment**

Androgen: oxymethalone

GCSF (severe neutropenia with recurrent infections) in SDS

Transfusion support

- **Monitor for hematologic and solid malignancy**

- **Bone marrow transplantation:** only cure for BMF

Reduced intensity conditioning regimen

Increased risk malignancy

How to Differentiate IBMFS from Immune AA



IBMFS	Immune AA
Younger age	Younger age or older age (bimodal)

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Slowly progressive/moderate cytopenia	Rapidly progressive/severe cytopenia

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-Congenital abnormalities -Multi-organ involvement (abnormal limbs, skin changes, early hair greying, syndromic facies, short stature, abnormal lung/liver)	No other organ involvement

How to Differentiate IBMFS from Immune AA

IBMFS	Immune AA
Younger age	Younger age or older age (bimodal)
Slowly progressive/moderate cytopenia	Rapidly progressive/severe cytopenia
-Congenital abnormalities -Multi-organ involvement (abnormal limbs, skin changes, early hair greying, syndromic facies, short stature, abnormal lung/liver) -Positive family history of malignancies, cytopenia at atypical early age, congenital abnormalities -Negative family history in AR, de novo mutation, incomplete penetrance	No other organ involvement Negative family history

How to Differentiate IBMFS from Immune AA

IBMFS	Immune AA
PNH clone: negative	PNH clone: positive or negative

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Cytogenetics: +1q in FA, isochromosome7q in SDS	Cytogenetics: -normal -del13q, trisomy 8, and loss of heterozygosity of short arm of chromosome 6 (6pLOH)

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Increased Hb F Telomere length: < 1 st percentile or < 10 th percentile with clinical features	Telomere length: normal or short (> 1 st percentile)
Chromosome breakage assay: positive	Chromosome breakage assay: negative

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Increased Hb F Telomere length: < 1 st percentile or < 10 th percentile with clinical features	Telomere length: normal or short (> 1 st percentile)
Chromosome breakage assay: positive	Chromosome breakage assay: negative
Genetic testing: -positive variants in specific genes	Genetic testing: -somatic mutations (5-70%)

When to Consider Germline Genetic Testing

- AA in adults age ≤ 40 years
- Genetic testing is **costly, time consuming, and not always available.**
- **> 90% of BMF is classified as immune.**
- **Treatment for patients with likely immune SAA need not be delayed while awaiting results from genetic sequencing.**
- However, if IBMFS is suspected. Appropriate tests for diagnosis should be performed before undergoing HSCT or ATG/CSA.

A 27-year-old woman was referred to investigate cause of bicytopenia.

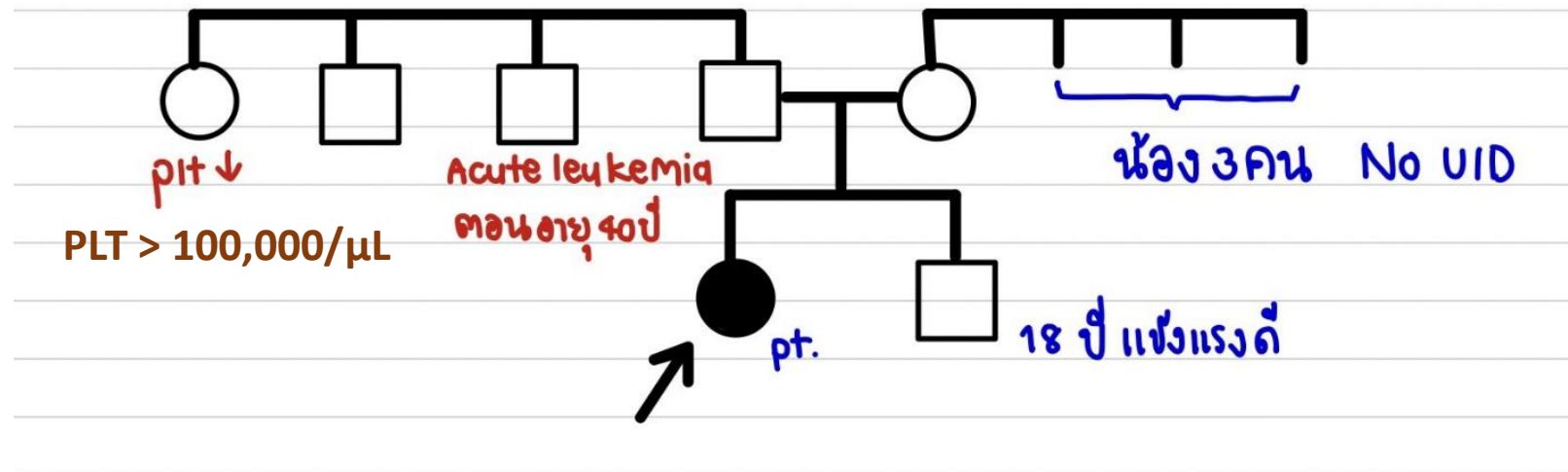
Visited SI

She had AUB without structural cause for 1 year. PLT was 70,000 - 90,000/ μ L.

At Siriraj
CBC: Hb 3-4.6 g/dL, MCV 86 fL, WBC 7,000/ μ L, N 80%, L 20%, PLT 55,000/ μ L,

Dx anemia from AUB with ITP

Family history



A 27-year-old woman was referred to investigate cause of bicytopenia.

Visited SI

1 month

Dx anemia from AUB with ITP

CBC: Hb 2.9-4.6 g/dL,
MCV 85 fL, WBC 7,000-
20,000/ μ L, N 80%, L 20%,
PLT dropped to
31,000/ μ L,
ARC 3,000-4,000/ μ L

PBS: NCNC RBCs, WBC,
N predominate, few
atypical lymphocytes,
decreased PLT

1st BM study:
inadequate
specimen

Cytogenetic study:
46, XX

NGS: LP variants in
ETV6 (VAF 48%),
IKZF1

She got PRC transfusion q 2-4 weeks.

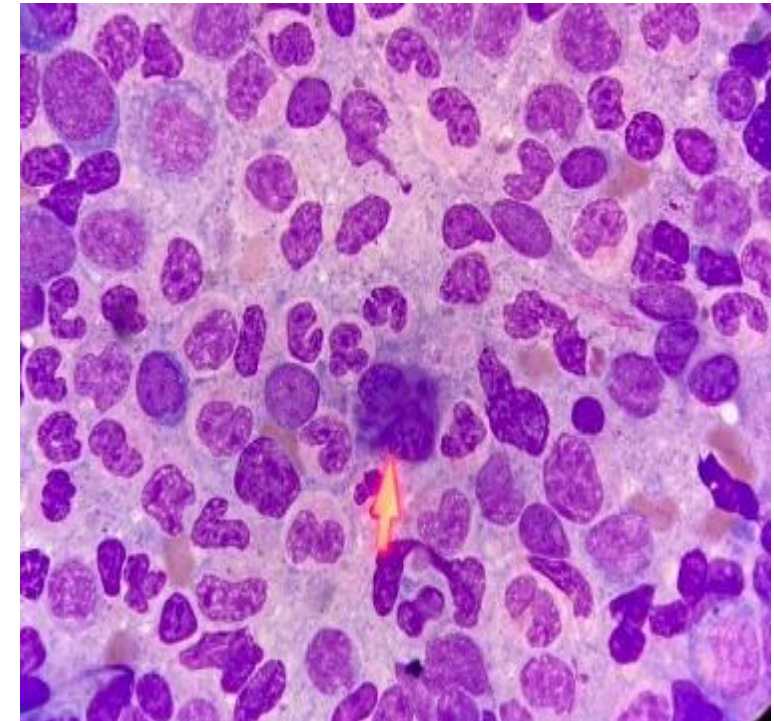
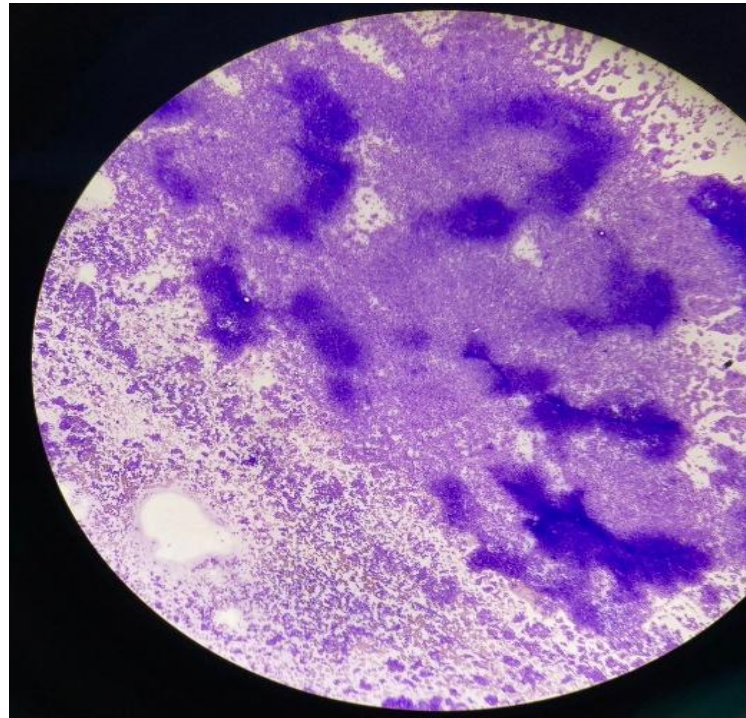
A 27-year-old woman was referred to investigate cause of bicytopenia.

6 months

2nd BM study: marked hypercellularity, **dyserythropoiesis**, normal Mfgk, **microMgk, immature myeloid precursors 10-15%**

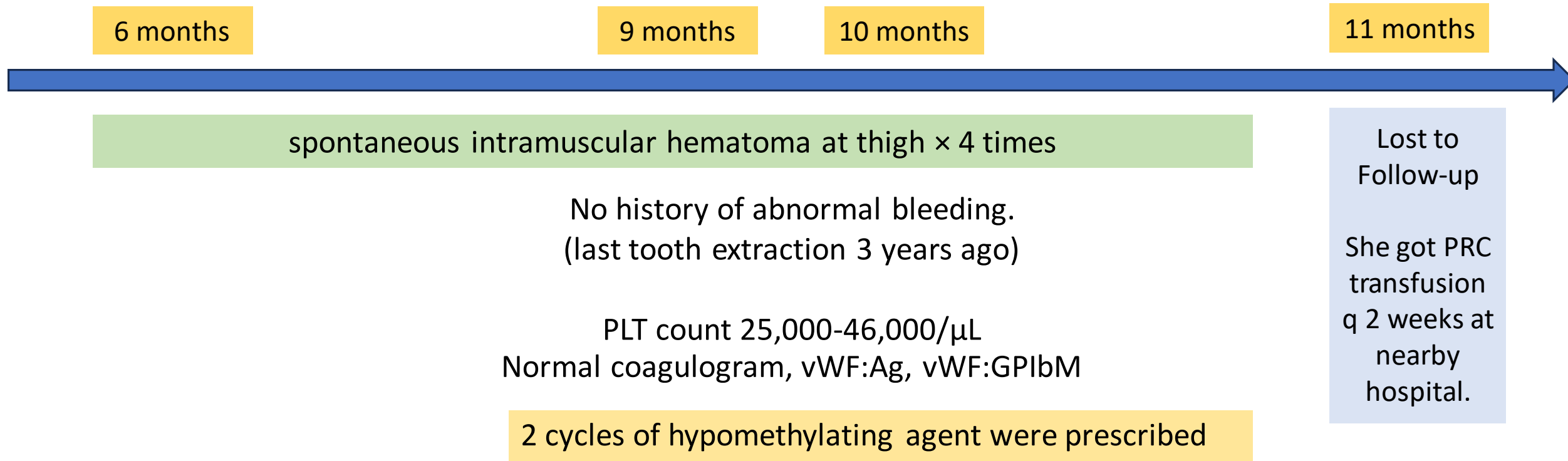
NGS: LP variants in **ETV6**, IKZF1, ASXL1

Cytogenetic study: 46,XX, r(18)(p11.2q23)[16]/46,XX, dic r(18;18)(p11.2q23;p11.2q23[1])/46,XX[3]



Dx secondary MDS, hereditary platelet disorders associated with germ line variants in ETV6

A 27-year-old woman with secondary MDS and hereditary platelet disorders related to ETV6.

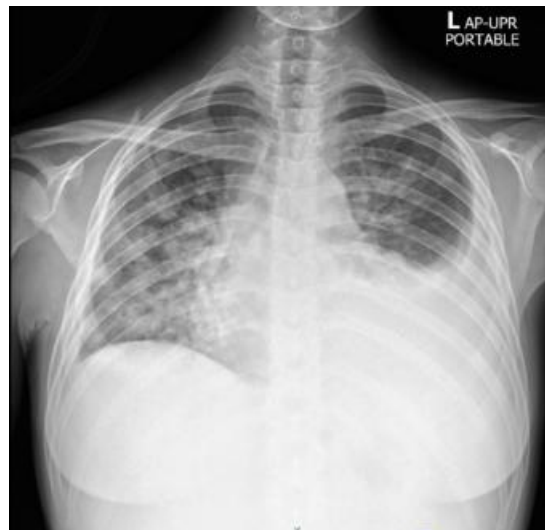


A 27-year-old woman with secondary MDS and hereditary platelet disorders related to ETV6.

15 months

At ER Siriraj hospital

Acute dyspnea
Productive cough
Orthopnea



CBC: Hb 3.8 g/dL, **WBC 79,960/ μ L**, N 25%, L 16%,
myeloblast 35%, band 12%,
Meta 4%, M 8%, PLT 10,000/ μ L

Eventually, she died from severe pneumonia with respiratory failure with septic shock.

Hereditary platelet disorders associated with germ line variants in ETV6

- AD
- Often present later in adolescence or adulthood
- Characterized by **mild thrombocytopenia** ($PLT > 75,000/\mu L$) with normal PLT size, **variable bleeding phenotype** (no bleed to mild bleed to bleeding out of proportion of low PLT), some have abnormal platelet aggregation
- Predisposition to hematologic malignancy (cumulative risk 30%)
B-ALL, MPAL, MN, MDS, AML, multiple myeloma, CMML

Take Home Message

- Distinguishing acquired from IBMFS is critical as it affects choice of therapy and donor selection especially patients who are indicated for HSCT.
- Diagnostic clues pointing towards IBMFS include young age, multi-organ disease, chronic onset of cytopenia, positive family history, cancer with highly sensitive to chemotherapy or radiation.
- Treatment with IST need not be delayed while awaiting genetic results unless a reasonable clinical suspicion for IBMFS exists.



Thank you for your attention