Pallor

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Case 1:

An 18-month-old male child who was previously healthy presents to the physician for routine well-child care. The mother states that the child is a "picky" eater and prefers milk to solids. In fact, the mother states that the patient, who still drinks from a bottle, consumes 64 ounces of cow milk per day. The child appears pale on examination.

Contributing factors in this case:

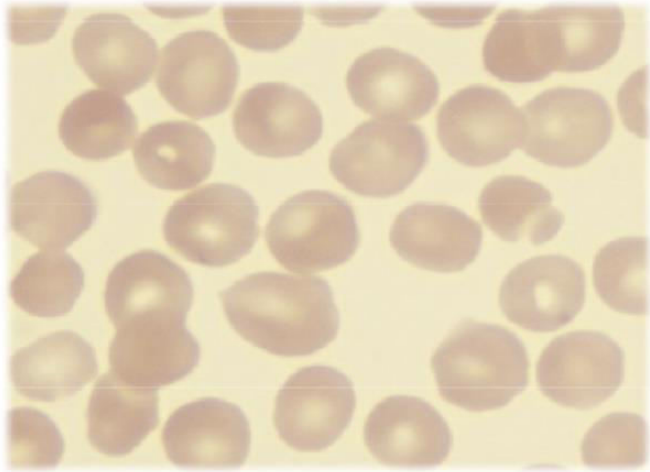
- **Excessive cow's milk intake that contains iron with low bioavailability**
- **Inadequate dietary iron intake**

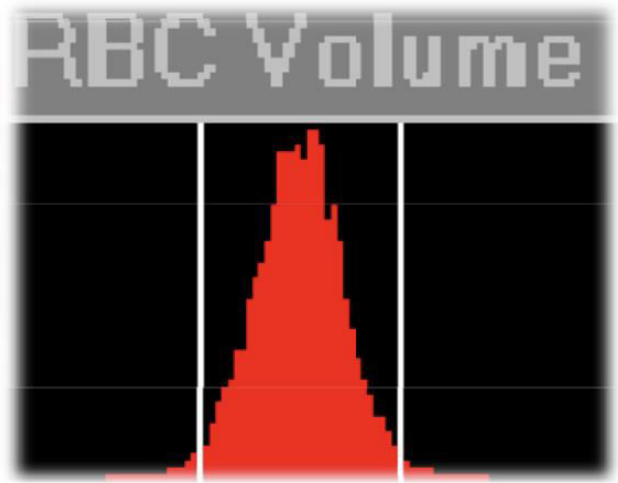
(Infants with decreased dietary iron typically are anemic at 9-24 months of age: caused by consumption of large amounts of cow milk and foods not enriched with iron; also creates abnormalities in mucosa of GI tract → leakage of blood, further decrease in absorption)

CBC Findings

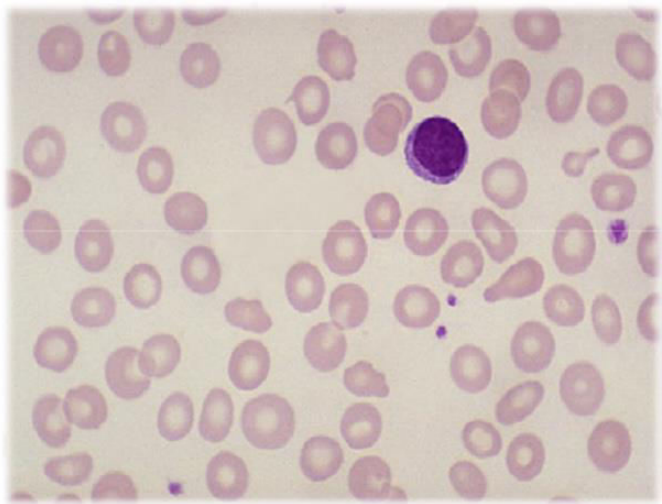
PARAMETER	VALUES	NORMAL VALUES
WBC	$4.8X10^3/\mu l$	$6\text{-}17\ X10^3/\mu l$
RBC	$2.8X10^6/\mu l$	$3.70\text{-}5.30\ 10^6/\mu l$
Hb	7.4gm/dl	10.5-13.5 gm/dl
Hct	21%	33 -49%
MCV	62fl	70-86 fl
MCH	20.8pg	23-31pg
MCHC	24.6%	30 - 36%
RDW-CV	18.2%	11.5-16%
Platelets	$219X10^3/\mu l$	$150\text{-}450X10^3/\mu l$

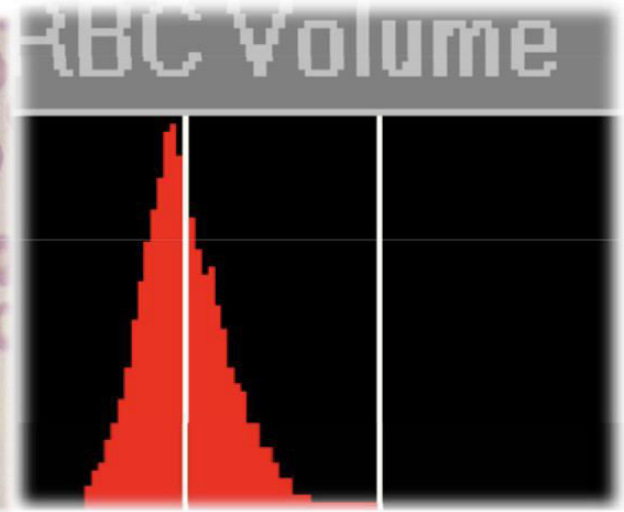
Peripheral smear examination





Normal





Patient

- ✓Micro hypo cells
- ✓RDW>18%

CBC and peripheral smear examination show microcytic hypochromic RBCs

Based on these findings, differential diagnosis are:

1. Iron deficiency anemia
2. Thalassemia
3. Anemia of chronic disease

Which investigations can be done further???

Iron Studies

PARAMETER	Sr. Iron	Ferritin	TIBC	% Transferrin Saturation
PATIENT	↓	↓	↑	↓

Reticulocyte Count

PARAMETER	Reticulocyte count
PATIENT	1.5%

What is the diagnosis???

Iron deficiency anemia

Definition:

Iron deficiency anemia is a microcytic hypochromic anemia and is commonly seen in children at 9-24 months of age.

Etiology: the majority of cases are caused by inadequate iron intake

1. Excessive cow's milk intake (higher bioavailability of iron in breast milk versus cow's milk or formula)
2. Inadequate dietary iron intake (so introducing iron-rich foods is effective in prevention)
3. Growth spurts at one year of age and puberty (during a growth spurt, the body's need for iron increases)
4. Malabsorption (e.g. celiac disease)
5. Blood loss (may be secondary to polyps, meckel diverticulum, inflammatory bowel disease, peptic ulcer disease, celiac disease or secondary to menorrhagia in adolescent girls)

Presentation:

1. Irritability and lethargy
2. Weakness and fatigue
3. Decreased exercise tolerance
4. Pica (repeated or chronic ingestion of non-nutritive substances, e.g., paint, dirt)
5. Anorexia and poor weight gain
6. Neurocognitive effects (poor concentration, diminished attention)
7. Tachycardia and tachypnea

Physical examination:

1. Pallor (noted especially on skin and on mucous membranes)
2. Koilonychia (spoon-shaped nails)
3. Angular stomatitis
4. Glossitis (seen in B12 and iron deficiencies)
5. Thin hair

Diagnostic laboratory tests:

1) CBC:

low Hb
low MCV & MCH
high RDW
normal WBCs
normal/high platelets
normal or low reticulocytes

2) Blood film:

microcytic hypochromic RBCs
Anisopoikilocytosis (variable sizes and shapes)

3) Iron study:

low ferritin (diagnostic), low serum iron, low transferrin saturation, high total iron binding capacity

Treatment:

1) Dietary counselling (decrease cow's milk intake, increase nutritional iron through iron rich foods such as meats and iron-fortified cereals)
2) Elemental iron (4-6 mg/kg/day orally divided once or twice a day)
3) IV iron in:
    1. Refractory cases
    2. Malabsorption

Note:

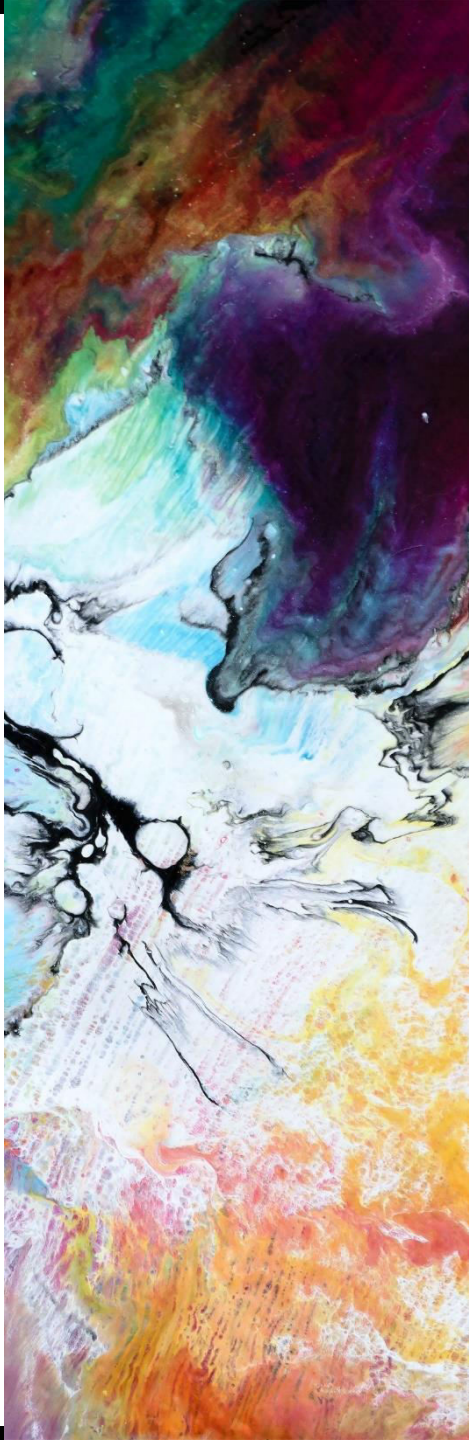
- Within 48-72 hours : peripheral reticulocytosis
- increase in Hb over 4-30 days
- Continue iron for 8 weeks after blood values normalize; repletion of iron in 1–3 months after start of treatment
- If the hemoglobin level fails to increase within 2 weeks after institution of iron treatment, careful re-evaluation for ongoing blood loss, development of infection, poor compliance, malabsorption, or other causes of microcytic anemia is required

Prevention:

- Bottle-fed infants should receive an iron-containing formula until 12 months of age
- Exclusively breast-fed infants older than 6 months of age should receive an iron supplement
- The introduction of iron-enriched solid foods at 6 months of age, followed by a transition to a limited amount of cow's milk and increased solid foods at 1 year, can help prevent iron- deficiency anemia
- Adolescent females who are menstruating should have a diet enriched with iron-containing foods

case 2:

previously healthy 7 months old boy of a consanguineous parents presented with complaints of gradual pallor and a yellowish discoloration of the sclera for 1 week duration.
The baby is also described by the parents as being less active and not growing well .
Positive family history of sibling with B-thalassemia major.
No fever , diarrhea or vomiting .
No history of exposure to a jaundice patient .
The urine is dark in color , but the stool is normal .
No recent travel history .



On examination :

by general inspection the patient was severely pale , hypoactive .
Jaundice was present , frontal bossing was present .
Vitals were normal .
Weight was 6 kg and length was 62 cm , both were below the 5^{th} percentile .
The abdomen was distended and with deep palpation there was hepatosplenomegaly.

Which labs need to be ordered ?

Result Released on : 07/11/2019 Released By: G.Gopina

Test Name	Result	unit	Reference Range	Remarks
HGB	7.07	g/dL	10.5 - 13.5	10.5 - 13.5
WBC	16.73	10*3/uL	6 - 17.5	6 - 17.5
RBC	3.73	10*6/uL	3.7 - 5.3	
PLT	297.80	10*3/uL	140 - 400	140 - 400
HCT	25.32	%	33 - 39	
MCV	67.93	fL	70 - 86	
MCH	18.97	pg	23 - 31	
MCHC	27.93	g/dL	31 - 35	
NEU%	15.67	%		
LYM%.	69.37	%		
EOS%	7.75	%		
MONO%	4.46	%		
BASO%	2.76	%		
NEU#	2.621	10*3/uL	1.5 - 8.5	1.5 - 8.5
LYM#	11.60	10*3/uL	4 - 10.5	
EOS#	1.297	10*3/uL	.1 - .8	
MONO#	0.75	10*3/uL	.2 - 1.3	
BASO#	0.46	10*3/uL	0 - .2	
RDW	22.55	%	11.5 -	
MPV	4.91	fL	7.2 - 1	
PCT	0.15	10*3/uL		
PDW	17.08	10*3/uL		

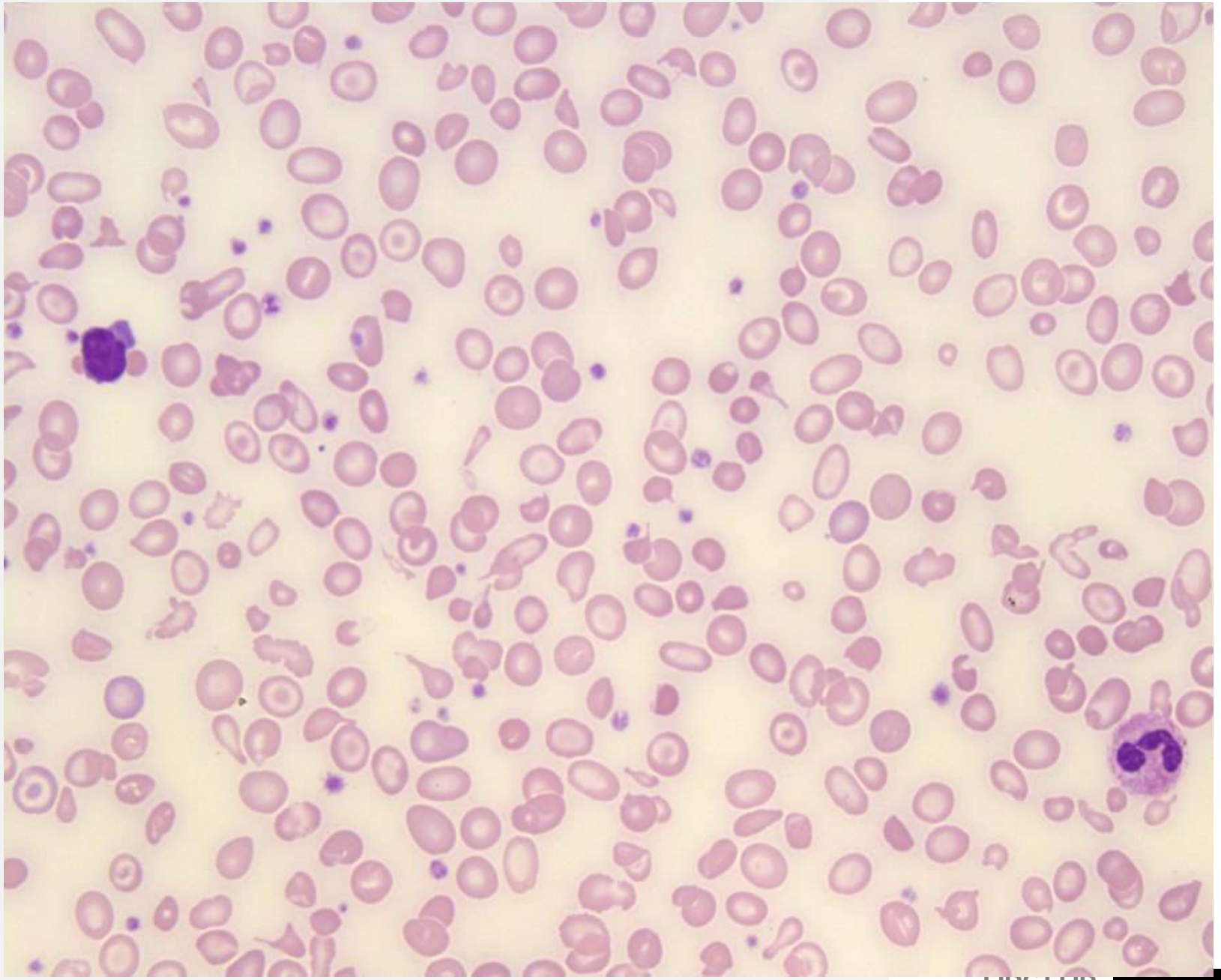
LAB REMARKS:
CBC done in RRBC mode. PS made for confirmation of cour

- **CBC : microcytic hypochromic anemia .**
- **Iron studies : normal serum iron and elevated ferritin.**
- **Liver function test : isolated indirect hyperbilirubinemia.**
- **What's next ?**

Blood film :

hypochromic, microcytic anaemia, nucleated red blood cells, target cells, and basophilic stippling , anisocytosis and poikilocytosis.

How to confirm the diagnosis ?



Haemoglobin electrophoresis : absence of HbA,
both HbF and HbA2 are elevated.

Hb. Disorders	Normal Hb			Variants	
	HbA mean/ range	HbA_2 mean/ range	HbF mean/ range	HbE mean/ range	HbS mean/ range
Thalassemia major	16.1 (3.1-53)	4.5 (2.5-8.6)	80.6 (42.6-92.8)	-	-
Thalassemia Intermedia	77.9 (57.5-88.4)	3.3 (2.6-10.4)	20.0 (10-30)	-	-
Thalassemia minor	93.6 (91.4-95.1)	5.3 (3.8-8.6)	1.6 (1.2-2.8)	-	-

Table 8: Mean and range of various haemoglobins in different hemoglobin disorders

Thalassemia

Thalassaemia is a **group of genetic disorders** that lead to **reduced haemoglobin** in red blood cells.

They are classified according to the **globin chain** which is affected and the **severity** of the resulting clinical picture.

thalassaemia is common in countries from the Mediterranean down to Africa and across to the Middle East and South East Asia.

In humans, there are **four alpha globin genes** located on **chromosome 16** used to make alpha chains. There are **two beta globin genes** located on **chromosome 11** used to make beta chains.

With reduced production in one type of globin chain, excess numbers of the other type of globin chain **accumulate** within red blood cell precursors. The accumulation of unpaired globin chains disrupts the cells' normal function and causes them to become **unstable.**

Alpha thalassaemia

- Silent carrier : no clinical significance , normal electrophoresis .
- Alpha thalassemia trait : mild microcytic hypochromic anemia .
- Hb H disease : with variable severity .
- Barts disease : hydrops fetalis or early neonatal death.

Beta thalassemia

- Thalassemia minor (trait): very mild anemia , blood film abnormalities , elevated HgA2 and F Hg .

- Thalassemia intermedia ; mild to moderate anemia m rarely require transfusion .

- Thalassemia major : sever anemia and the patient is transfusion dependent .

Clinical features :

- **Severe anaemia**: becomes apparent at 3-6 months after birth when the switch from foetal haemoglobin (HbF) to adult haemoglobin (HbA) occurs.
- Jaundice
- **Splenomegaly and hepatomegaly**: occur due to excessive red blood cell destruction and extramedullary red blood cell production.
- **Features of bone marrow expansion :**

Thalassaemic facies: occurred when bone expansion affected cheekbones and forehead.
Predisposition to fractures: due to an impairment of bone structural integrity.
Bossing of the skull with a 'hair on end' appearance on X-ray .

Management :

Regular red cell transfusions. Patients usually require 2-3 units every 4-6 weeks to maintain haemoglobin levels over 10g/dL and suppress erythropoiesis (the production of red blood cells).

Splenectomy can be considered to reduce blood requirements.

Monitoring of iron status and iron chelation therapy (e.g. desferrioxamine) is essential to avoid iron overload.

Folic acid (5mg daily) to replace folate stores which are used up more quickly because of increased red cell turnover.

BONE MARROW TRANSPLANTATION.

Case 3:

- 6 year-old male, brought to the clinic by his mum because he feels tired all the time.
- History of headaches and problems concentrating.
- History of neonatal jaundice.
- History of pallor and subsequent jaundice worse at times of intercurrent illness.
- Family history: his father had splenectomy when he was 26 YO, and his uncle had cholecystectomy when he was 30.

- **<u>On physical exam :</u>**

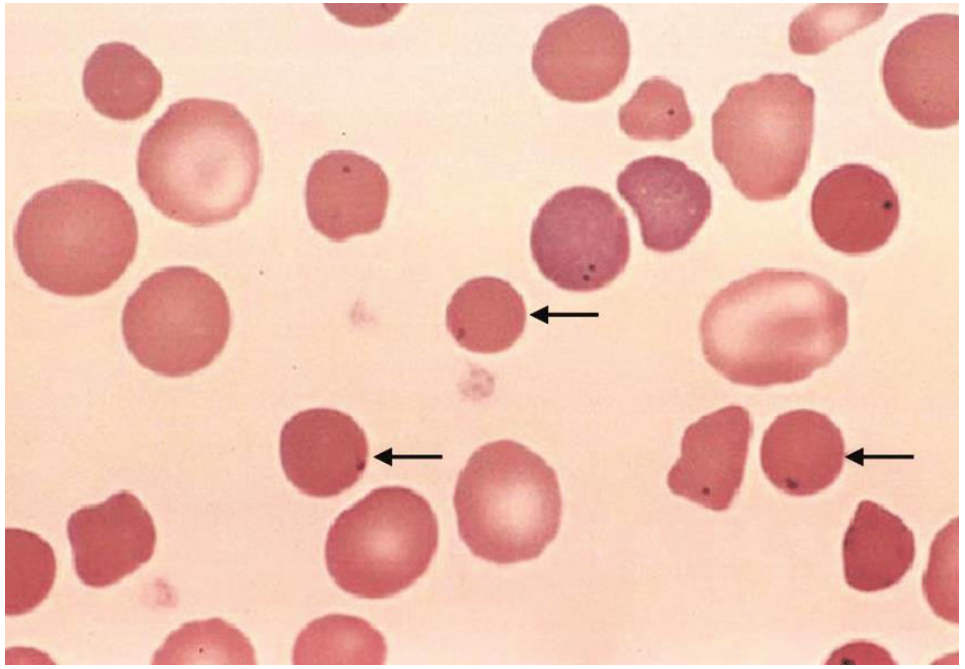
- Conscious, dizzy and tired
- Afebrile, vitals stable
- Pallor +ve
- Scleral icterus
- Splenomegally

- What laboratory investigations would you do?

Laboratory investigations

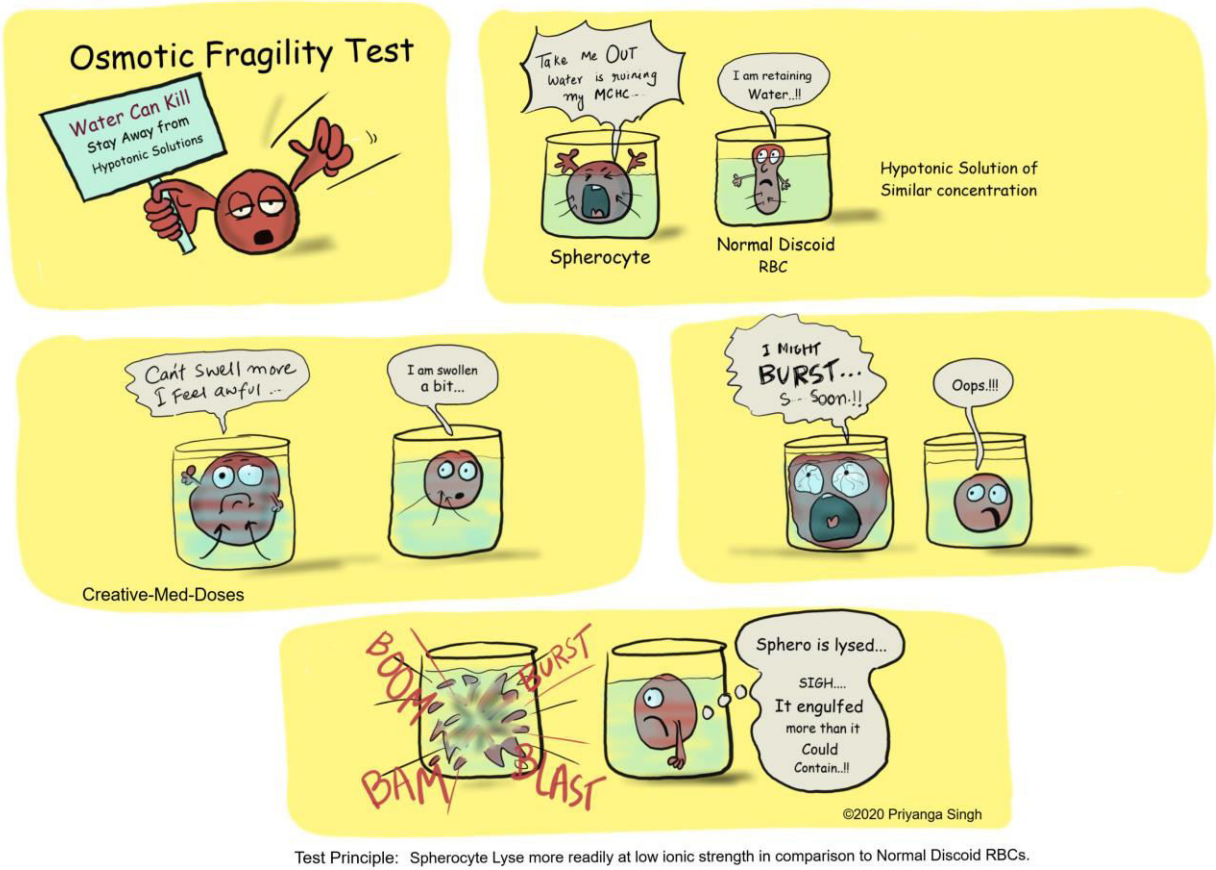
- **Cbc:**
- WBC’s: 9000/µL
- RBC count: 3.2 million/ µL
- Hb: 9.5 mg/dl
- Hct: 27%
- MCV: 80 fl
- MCHC: 37%
- RDW: 20%
- Plt: 290 x10 3/µL
- **Reticulocyte count:** 5%

- Indirect Bilirubin: elevated
- Serum LDH: elevated
- Serum haptoglobin: normal
- Peripheral blood smear: spherocytes
- Direct coombs test (DAT): negative



- What's your ddx?
- What would you do next to confirm a diagnosis?

- Osmotic fragility test: increased



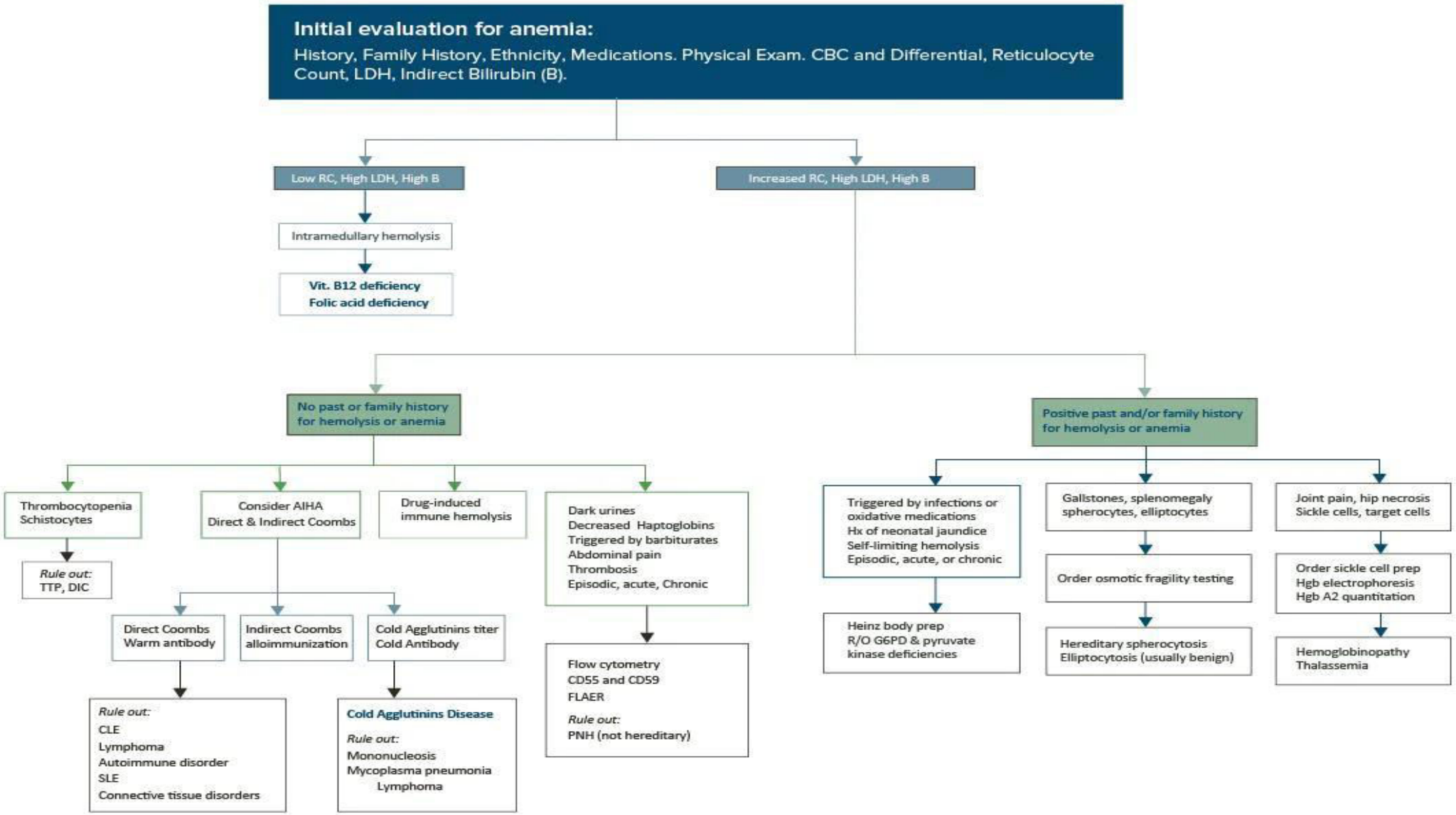
Test Principle: Spherocyte Lyse more readily at low ionic strength in comparison to Normal Discoid RBCs.

Hemolytic anemia

- Hemolysis is the premature destruction of erythrocytes. A hemolytic anemia will develop if bone marrow activity cannot compensate for the erythrocyte loss. The clinical severity of the anemia depends on whether the onset of hemolysis is gradual or abrupt as well as the extent of erythrocyte destruction.
- Hemolytic anemia represents approximately **5%** of all anemias.
- Hemolysis can occur intravascularly or extravascularly.
- Autoimmune hemolytic anemia and hereditary spherocytosis are examples of **extravascular** hemolysis because the red blood cells are destroyed in the spleen and other reticuloendothelial tissues.
- **Intravascular** hemolysis occurs in hemolytic anemia due to:

1. G6PD deficiency.
2. TTP
3. DIC
4. Transfusion of ABO incompatible blood
5. Pyruvate kinase deficiency.

Algorithm: Flow Chart for the Diagnosis of a Hemolytic Anemia



Hereditary spherocytosis

- Hereditary spherocytosis (HS) is a familial hemolytic disorder associated with a variety of mutations that lead to defects in red blood cell (RBC) membrane proteins.
- HS is caused by variants in one of the five genes (ANK1, SPTA1, SPTB, SLC4A1, and EBP42) that encode the erythrocyte membrane proteins ankyrin, alpha-spectrin, beta-spectrin, band 3, and band 4.2, respectively.
- HS is usually transmitted as an autosomal dominant trait, and the identification of the disorder in multiple generations of affected families is the rule.
- An autosomal recessive mode of inheritance also occurs, as indicated by descriptions of families in which apparently healthy parents have had more than one affected child.

Clinical presentation

- As in other chronic hemolytic states, the signs and symptoms of hereditary spherocytosis (HS) include mild pallor, intermittent jaundice, and splenomegaly. However, signs and symptoms are highly variable.
- Anemia is usually mild to moderate, but is sometimes very severe and sometimes not present.
- Splenomegaly is the rule in HS.
- Other important clues are jaundice and upper right abdominal pain indicative of gallbladder disease.
- Gallstones, resulting from excess un-conjugated bilirubin in bile, may be found in very young children, but the incidence of gallstones increases markedly with age.

Investigations

- 1.Complete blood cell count
- 2. Reticulocyte count
- 3. Mean corpuscular hemoglobin concentration (MCHC)
- 4. Peripheral blood smear
- 5. Lactate dehydrogenase (LDH) level
- 6.Haptoglobin
- 7.Fractionated bilirubin
- 8. Combs testing

Management

- folic acid supplementation 1 mg/d.
- Leukocyte-depleted packed red cell transfusion for severe erythroblasto-penic crisis.
- Splenectomy is the definitive treatment for HS.

-Vaccination against pneumococcus and H influenzae must be administered to patients prior to splenectomy.

-Splenectomy may fail to control HS because of any of the following:

1. An accessory spleen.
2. Accidental autotransplantation of splenic tissue into the peritoneum during surgery.
3. Another hemolytic disorder.

- Periodic ultrasonic evaluation of the gallbladder should be performed because Bilirubin gallstones are found in approximately 50% of patients with HS and frequently are present in patients with very mild disease.

Case 4

- Eight years old girl presented with **bleeding from gums and petechiae** over the body with a **history of failure to thrive**, **pancytopenia** *for* six months ,first born child of a consanguineous marriage
- She was admitted as a case of pancytopenia for investigations.

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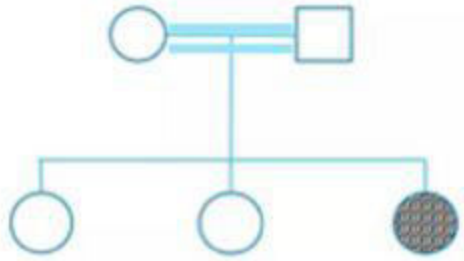
Past medical history:

- The age of presentation is 7 years old (since almost a year)
- Initially presented with pallor, epistaxis and breathlessness.
- Recurrent respiratory symptoms like fever, cough, breathlessness. Similar complaints like pallor, easy fatiguability in the past 6 months
- Packed cells and platelet transfusions every month since 4 months.

Perinatal history
Antenatal history: Booked case, had regular antenatal check ups.
Natal history: Normal vaginal delivery, term baby, Birth weight: 2kgs
Cried immediately after birth, breast fed till 6 months
Postnatal history: uneventful

Immunisation history
• Immunization done as per schedule
BCG scar present over left upper arm

Family history :
no family history of hematological disorder
consanguinity marriage



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no known allergies
no drugs are taken regularly

Physical Examination:
On general physical examination child was conscious, alert and well oriented in time, place and person lies supine , she was **pale**

Vitals were normal Vitals: Pulse rate - 110 beats per min \Respiratory rate - 20 breaths per min \Blood pressure - 110/70 mm of Hg \Temperature - Afebrile

her height was 92 cm (<5th %) consistent **with short stature**, weight was 12.8 kg (<5th %).

• **Many petechial hemorrhages** cover her chest and legs was noticed also Several bruises are found on her legs and thighs

with patches of **hyperpigmented areas(Café-au-lait spots)**

on skin also She had **absent thumbs of both hands**

• There's no lymphadenopathy or hepatosplenomegaly.
Rest of the physical and systemic examination was unremarkable

Lab test was ordered on admission

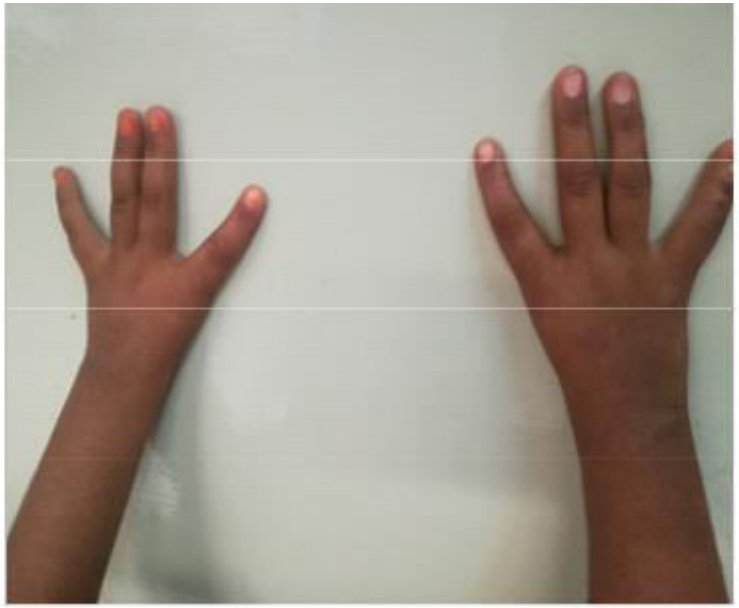
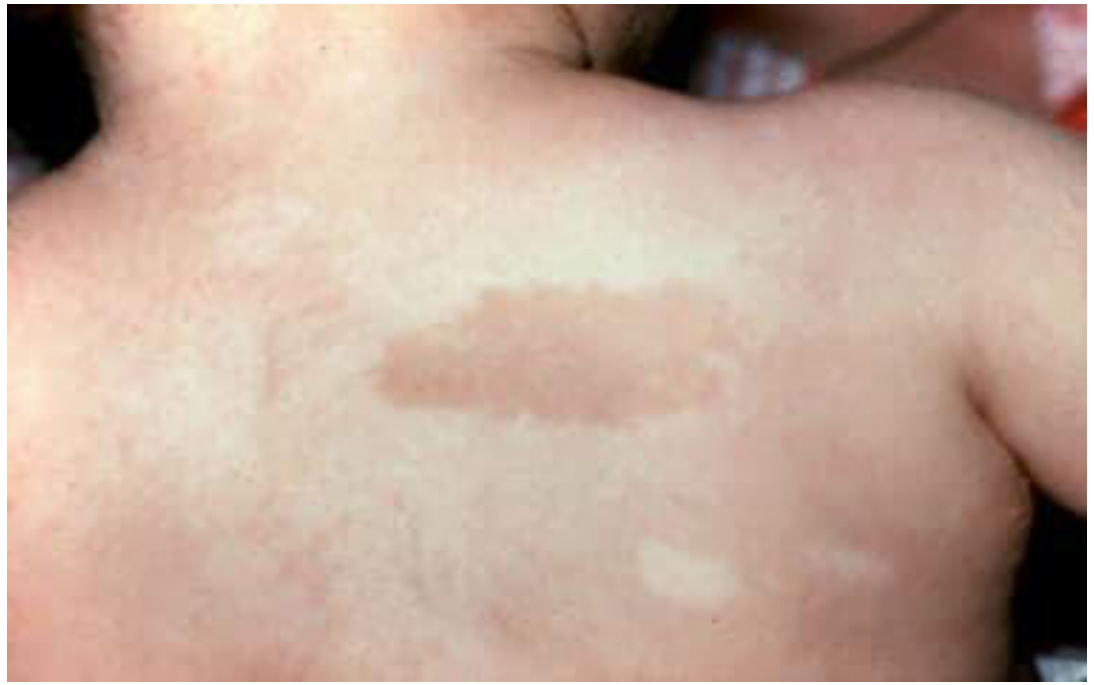


Figure 1: Absent thumb of both hands



Laboratory investigations showed:

- Hemoglobin of 4.2 g/dl
- White cell count 1.9*103 /ul
- Platelets count of 72*1000 / UL
- Neutrophil count was 0.4 (Absolute Neutrophil Count was 400).

- Reticulocyte count – reduced
- liver enzymes were all normal.
- TBC decreased
- Iron : Serum iron levels
- normal TIBC-normal
- Vitamin b12 (serum) – normal
- Bleeding time - 8 min
- Clotting time - 10mins

- **Peripheral smear examination**: Hypochromic macrocytic picture and leucopenia, thrombocytopenia
- Differential leukocyte count revealed 38% neutrophils, 56% lymphocytes, 03% monocytes, 02% myelocytes and 1% eosinophils.

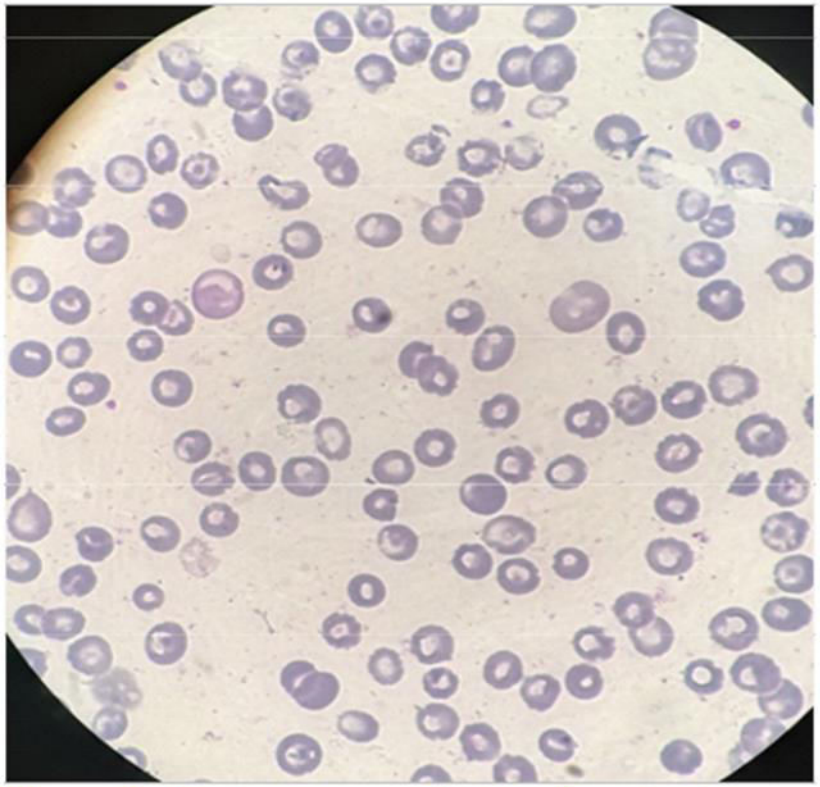


Figure 2: showing macrocytic hypochromic picture with target cells.

- **Radiological findings:**
- Ultrasound abdomen and pelvis showed horse shoe kidney with bilateral empty renal fossa

- Echocardiogram was done and it was unremarkable.

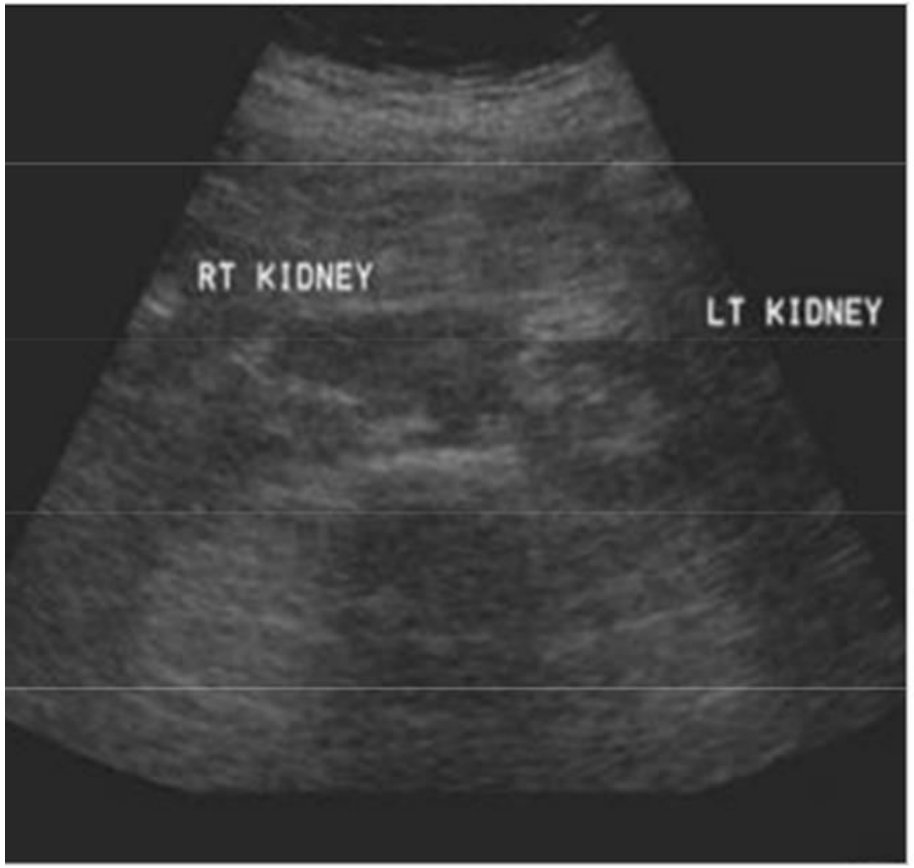


Figure 3: showing horse shoe kidney on ultrasound

Bone marrow examination: Bone marrow aspirate and trephine was taken from posterior superior iliac spine which showed hypocellular bone marrow fragments with increased fat spaces and depressed erythropoiesis, myelopoiesis and megakaryopoiesis

- There was no fibrosis and no blasts.

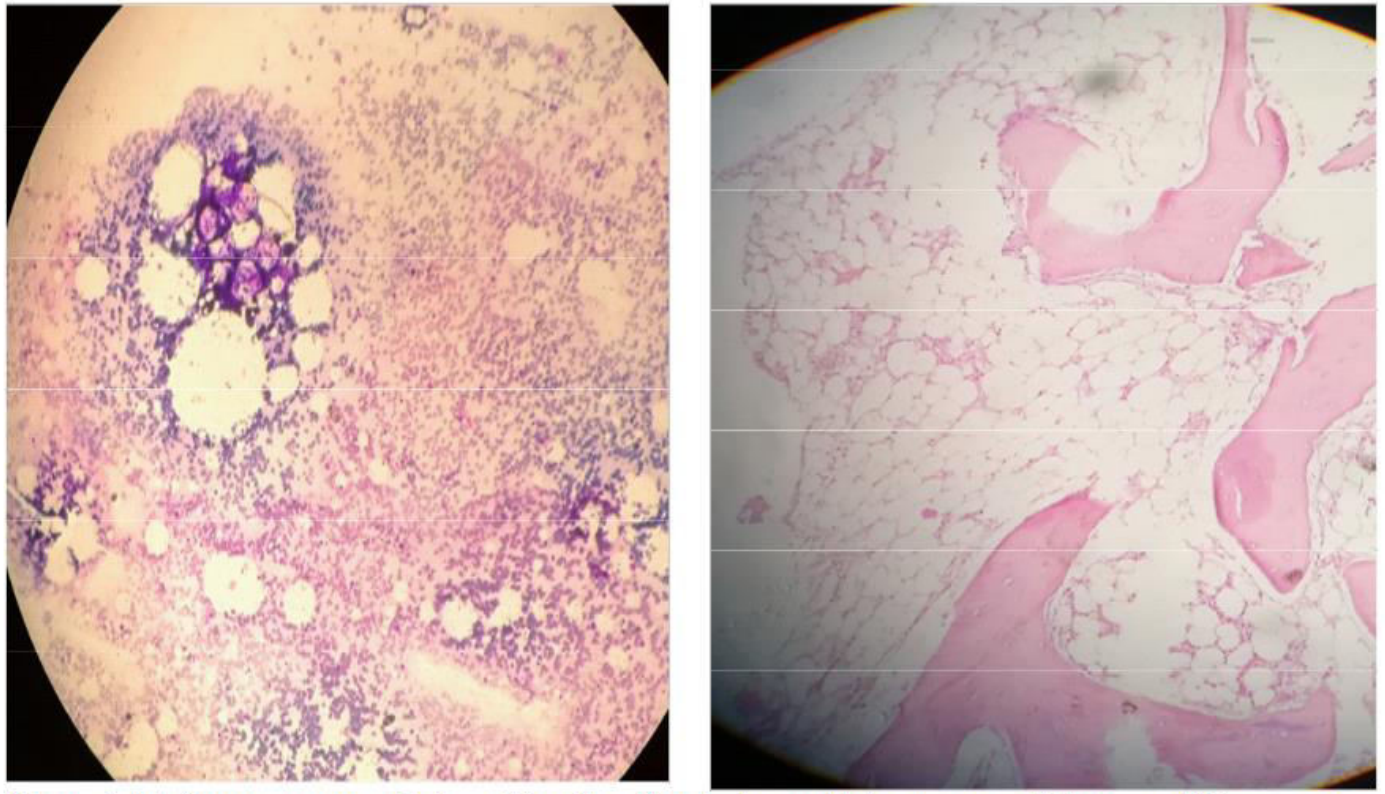


Figure 4 & 5: Bone marrow aspirate and trephine showing hypocellular marrow with increased fat spaces on

- **Cytogenetic studies:**

Cytogenetic studies were done to confirm the suspected diagnosis chromosomal breakage by using Mitomycin C and Diepoxybutane

chromosomal breakage studies were **positive** after exposure to DNA crosslinking agent mitomycin C.

DDX

- Congenital aplastic anemia
- Acquired aplastic anemia
- Acute myelocytic leukemia

Diagnosis:

Fanconi Anemia

Fanconi anemia (FA)

- Fanconi anemia (FA) is a rare inherited bone marrow failure syndrome, Autosomal recessive characterized by pancytopenia, predisposition to malignancy, and physical abnormalities including short stature, microcephaly, developmental delay, café-au-lait skin lesions, and malformations belonging to the VACTERL-H association.
- Result of genetic defect in cluster of protein responsible for DNA repair
- Diagnosis is usually made in childhood, although diagnostic delays and variable disease manifestations are common, and some individuals may be diagnosed with FA in adulthood.
- Many patients eventually develop acute myelogenous leukemia at an early age.

- Management of patients with FA is challenging because hematopoietic stem cell transplantation (HCT) is curative for bone marrow failure and hematologic neoplasms but not for the non-hematologic features.

- **Treatments include:**
- Bone marrow transplant.
- Hematopoietic (blood-stimulating) growth factors are used to stimulate WBC production.
- Androgens: stimulate the production of RBCs and platelets.
- Future: gene therapy
- Genetic counseling

•Prognosis

- The prognosis of Fanconi anemia is poor. Severe aplastic anemia is the main cause of mortality that leads to death before 10 years of age in the absence of a diagnosis.
- Survival has been improved in developed countries due to a reduction in mortality by bleeding, or infection complications.
- However, living well into adulthood has increased the chances of cancer development.
- Most of the individuals eventually develop acute myelogenous leukemia. Regular monitoring of patients is needed for cancer in those who have undergone a bone marrow transplant. Most of the patients have other associated birth defects, such as developmental delay, kidney problems, and microcephaly.

Clinical Case

Acute lymphoblastic leukemia

History of presenting complaints

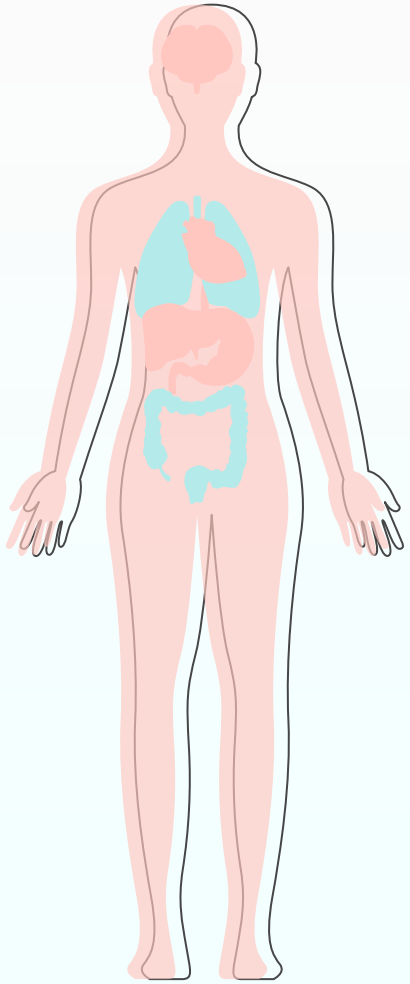
A 3 year old male patient admitted to The King Hussein Cancer Center on 15th June 2023 due to fever for 1 week associated with bone pain for 2 month.

Hussam was previously healthy until he started experiencing pain in his left knee early one morning two months ago. He couldn't sleep that night due to the pain, so his mother took him to the emergency room where an X-ray was performed (which came back normal). He then went home, but the pain got worse and he was unable to walk three days before being admit. However, there was no history of trauma noted.

The fever was on and off, low grade and associated with chills and rigor. The patient also complaining from anorexia and exercise intolerance.

PHYSICAL EXAMINATION

- Pallor
- Bruising and Petechial skin lesion
- Hepatosplenomegaly
- Lymphadenopathy
- Pin point tenderness over the bone



INVESTIGATION

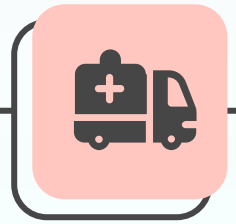
1)Full Blood Count

Shows pancytopenia, indicating bone marrow Suppression or failure

Blood Component	Result	Normal Range	Remarks
WBC	1.06	4-11 x 10^9/L	Low
Hb	5.5	11.5-18.0 g/dL	Low
Platelet	20	150-450 x 10^9/L	Low
Hematocrit	19.5	36-56 %	Low
MCV	76.6	79-96 fL	Low
MCH	21.6	27-32 pg	Low
MCHC	28.3	30.0-36.0 g/dL	Low
RDW	17.5	10-16.5%	Increased
Neutrophil (absolute; %)	0.21 ; 19.7	2.9-7.9 x 10^9/L; 87.4 %	Low
Lymphocyte (absolute; %)	0.77 ; 72.6	1.8-4.0 x 10^9/L ; 26.0%	Low ; Increased

Differential Diagnosis :

01

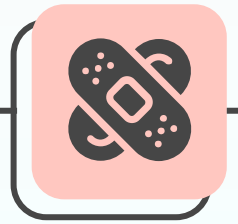


Leukaemia

02

Aplastic Anemia

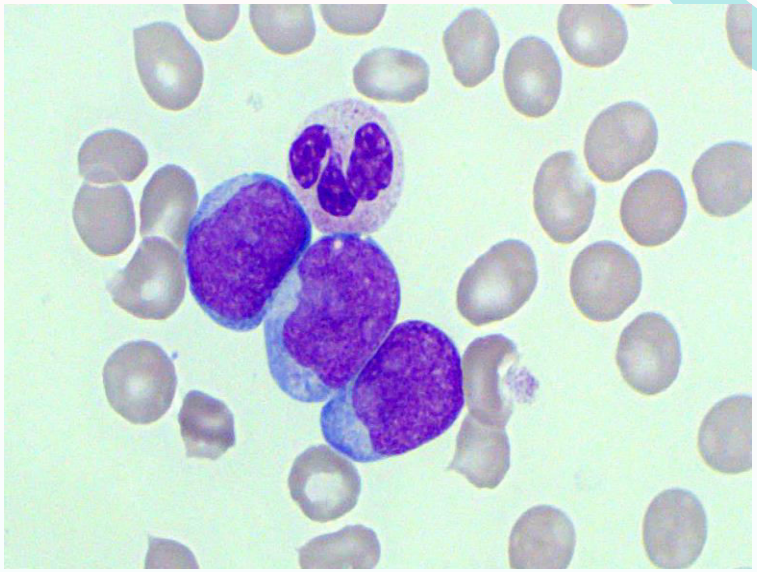
03



Fifth disease (parvovirus B19)

INVESTIGATION

2)Blood Film



- RBC: Microcytosis with anisopoikilocytosis.
- WBC: Markedly reduced, Shows peripheral blasts.
-
- PLT: Reduced. No platelet clumping.

3)Bone marrow aspiration

The smear show more than 90% blasts of nucleated bone marrow cells suggestive of Acute Lymphoblastic Leukemia .

Correlating the bone marrow aspirate and immunophenotyping, these findings consistent with precursor B Acute Lymphoblastic Leukemia.

Final Diagnosis

Juvenile arthritis secondary to
Acute lymphoblastic leukemia

Leukemia

- Leukemia is a malignant disorders of hematopoietic stem cells ends with accumulation of abnormal cells in the bone marrow.
- Leukemia is the most common childhood cancer, accounting for 31% of all pediatric malignancies.

- **Types** :
- 1) depend on the duration: Acute vs chronic
- ACUTE : proliferation of primitive stem cells leading to an accumulation of blasts, which lead to bone marrow failure.
- CHRONIC : the malignant clone is able to differentiate resulting in accumulation of more mature cells.

- 2) depend on the cell line affected : Myeloid or Lymphoid

Acute lymphoblastic leukemia

Peak age

2-3 years

Gender

Male more common than female

Predisposing conditions

1) Down syndrome
2) Fanconi anemia
3) Ataxia telangiectasia
4) Wiskoot-Aldrich syndrome
5) Blackfan-Diamond syndrome
6) Siblings (2-4 times greater for twins)
7) Radiation

Classification

1) Pre-B ALL(most common and better prognosis) 85%
2) T-cell ALL 15%.
3) Burkitt (mature B) ALL 1%.

Prognosis

5 year survival rate more than 85%

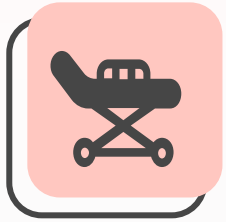
SYMPTOMS

- Initially, non specific symptoms : anorexia, irritability, malaise, fatigue, weight loss.
- Persistent infection and fever (low healthy white blood cells).
- Pallor (lack of red blood cells).
- Abnormal bruising(low platelets).
- Bone or joint pain(bone marrow filling with leukemia cells).
- History of upper respiratory infection in preceding 1-2mounth.
- Respiratory distress (sever anemia, mediastinal node).
- CNS involvement(headache, seizures).

SIGNS

- Hepatomegaly.
- Splenomegaly.
- Lymphadenopathy.
- Purpuric and petechial rash.
- Testicular mass.
- Pin point tenderness.
- Papilledema

DIAGNOSIS



- CBC (anemia, thrombocytopenia, leukocytosis often)
- Blood film (peripheral blasts)
- Bone marrow aspiration(hypercellular replacement of normal cells by blast cells which more than 25%) and Flow cytometry.
- Lumber puncture and CSF analysis.
- Chromosomal analysis (good : TEL-AML1, Hyperdiploidy) (bad : Philadelphia).
- Chest X-ray for mediastinal mass
- High lactate dehydrogenase
- Renal profile(tumor lysis syndrome)

MANGMENT

- Divided into three phases:

1) Remission induction.
2) Remission consolidation.
3) Remission maintenance.

Duration is 2-3 year.

** The most important prognostic factor is early response to chemotherapy.

- Chemotherapy agents :

Methotrexate, corticosteroids, vincristine, daunomycin.

For maintenance: mercaptopurine and oral methotrexate.

- Supportive therapy for bone marrow failure.