HEMATOLOGY
&LYMPH SYSTEM

Problem Based Learning sheet

Number	2
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Clinical hematology is divided into four subjects :

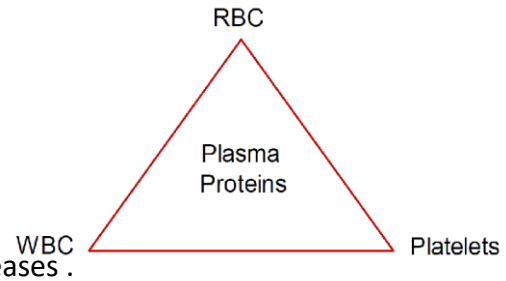
1- Benign hematology
   - Anemia
   - Benign WBC disorders
   - Bone marrow disorders (non-malignant)

2- Malignant hematology
   - Leukemia: acute/chronic
   - Lymphomas: NHL/ HL
   - Plasma cell disorders
   - Myeloproliferative neoplasms (MPN)
   - Myelodysplastic syndrome (MDS)

3- Hemostasis and thrombosis
   - Platelet disorders
   - Thrombosis
   - Anticoagulation
   - Hemophilias

4- Transfusion medicine

Four components of blood are :



The cellular elements of blood

(RBCs,WBCs and platelets) swim in plasma .

Problems affect any of these components >> cause different diseases .

Diseases of RBCs

Less RBC>>>Anemia
Because of Low production OR Increase destruction

More RBC>>Erythrocytosis or Polycythemia
**Not mentioned :High amount of RBC is called Erythrocytosis, while an increment in all types of blood cells is called Polycythemia!

Anemias are extremely important and to diagnose anemia we should do CBC "Complete Blood Count" which is a blood test
that measures several components and features of blood, including:

	Men	Women
Hemoglobin (g/dL)	14-17.4	12.3-15.3
Hematocrit (%)	42-50%	36-44%
RBC Count (10^6/mm^3)	4.5-5.9	4.1-5.1
Reticulocytes	1.6 ± 0.5%	1.4 ± 0.5%
WBC (cells/mm^3)	~4,000-11,000	
MCV (fL)	80-96	
MCH (pg/RBC)	30.4 ± 2.8	
MCHC (g/dL of RBC)	34.4 ± 1.1	
RDW (%)	12-15%	

If **hemoglobin** is less than its normal range >>**Anemia**
If **hemoglobin is** higher than its normal range >>**erythrocytosis or polycythemia**
Hemoglobin normal range is higher in men than women

To know the **type of anemia** we look at **MCV**
"mean corpuscular volume" is the average volume of red blood cells, normal range is 80-96 fL/cell, less than 80 is called **Microcytosis** while above 96 is called **Macrocytosis.**

In iron deficiency anemia or thalassemia MCV is 70 fl/cell >> microcytosis
Then how to differentiate between them**, we look at RDW**
"red blood cell distribution width" is another important thing to pay attention to, normal range is 12-15%, if it's higher then there is wide variation, a condition called Anisocytosis "**RBC are unequal size**"

MCV: 70 RDW: 14

if MCV is 70 and RDW is 14 (in normal range)>> thalassemia (all cells have the same size)

MCV: 70 RDW: 18

if MCV is 70 and RDW is 18 >> iron deficiency anemia (cells have unequal size)

Before official marriage, test for thalassemia should be performed, using CBC.
if both hemoglobin and MCV are low than normal
then we look at RDW if it is in normal range >> this person has thalassemia trait and if both the woman and the man carry thalassemia trait >>they can't get married.

WBC

- **High WBC** (Leukocytosis):

Because of:

Infection (Leukemoid reaction)
Or Inflammation
Or Leukemia

- **Low WBC** (Leukopenia)
- **Normal in number** (Dysfunction):
  Because of Immunedeficiency

Platelets

- **Low Platelets** (Thrombocytopenia) due to:
  Increased destruction
  Decreased production
- **High Platelets**
  Thrombocytosis because of Inflammation
  If inflammation is not the underlying cause then it's called Essential thrombocythemia
- **Normal in number** (Dysfunction)

Plasma Proteins

- **High >>**Hyperviscosity
- **Low:**

Low Coagulation factors can lead to Bleeding

Low Albumin: can lead to edema

Let's start with the cases:

Case 1:

Elderly with low back pain

-68-year-old male patient

-Complains of back pain for several months

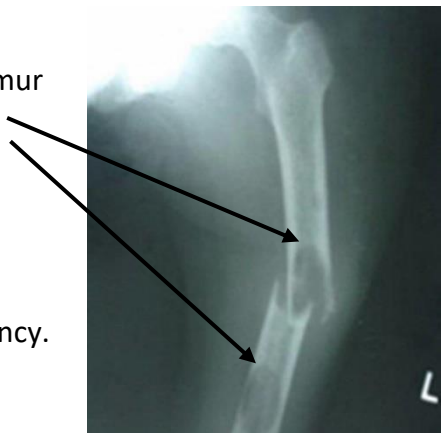
-Fractured his left leg two days ago.

As you can see in X-ray, there are two lytic lesions in a femur and the fracture is in

one of them

If the fracture is in an abnormal bone (lytic lesion) >> pathological fracture

Pathological fractures are secondary to tumor or malignancy.



Investigations

Guideline Values for Complete Blood Count		
Component	**Normal values for men**	**Normal values for women**
Red Blood Cells	4.4-5.8 million/ml	3.9-5.2 million/ml
White Blood Cells	3800-10.800/ml	3800-10.800/ml
Platelets	130.000-400.000/ml	130.000-400.000/ml
Haemoglobin (Hb)	13.8-17.2 g/100 ml	12.0-15.6 g/100 ml
Neutrophils	1500-7800 cells/ml	1500-7800 cells/ml
Eosinophils	50-550 cells/ml	50-550 cells/ml
Basophils	0-200 cells/ml	0-200 cells/ml
Lymphocytes	850-4100 cells/ml	850-4100 cells/ml
Monocytes	200-1100 cells/ml	200-1100 cells/ml
MCH	27-32 pg (picograms)	27-32 pg
MCHC	28-36 g/100 ml (red blood cells only)	28-36 g/100 ml (red blood cells only)
MCV	80-94 fl (femtolitres)	80-94 fl

Hemoglobin 7.3 g/dL >>**low**>>anemia ,

WBC count is normal ,

platelet count is normal,

ESR is 120 mm/hr which is **very high** "erythrocyte sedimentation rate normal range under 20-30".

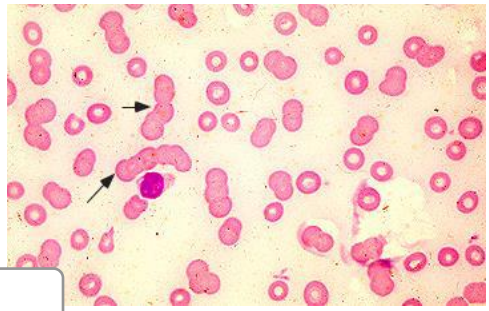
Blood urea nitrogen is 115 mg/dL **very high** "normal range 30-40".

Creatinine 3.2 "**normal is 1**"

Total serum protein is high, **calcium level is high** 13 mg/dL "normal "5-10"

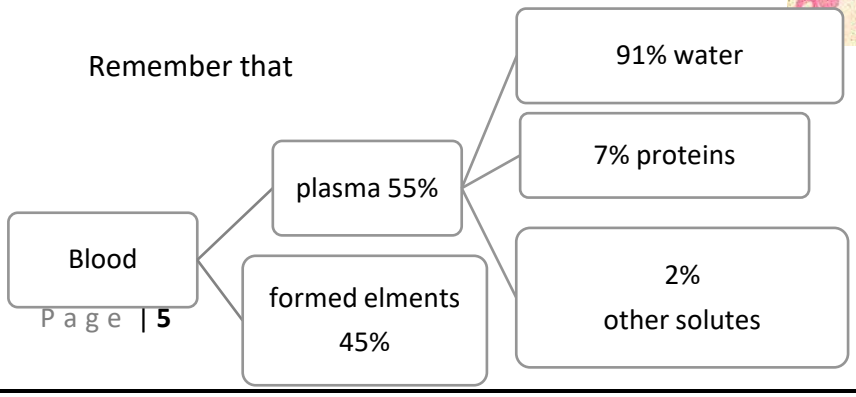
Blood film shows multiple erythrocytes lining up together in a form called Rouleaux formation (this formation is due to increase serum proteins)

Rouleaux formation is a characteristic of plasma cell disorders (when you see this you must think of **plasma cell disorder** or **multiple myeloma**).

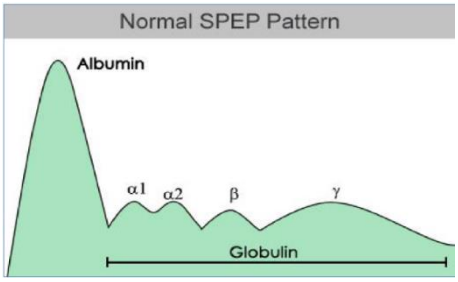


Serum Proteins Electrophoresis (SPEP)

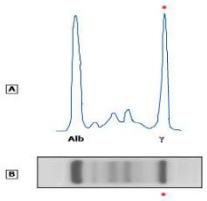
Remember that



Main proteins of plasma are globulins and albumin.
Globulins types :alpha 1,alpha 2,beta ,gamma .
Gamma globulins are immunoglobulins produced by plasma cells .
They are IgM,IgD,IgG,IgA,IgE



In normal SPEP , γ globulins zone is flat

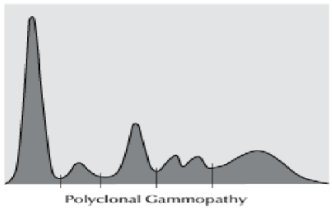


If there is a spike in the gamma globulins this indicates for <u>plasma cell disorders.</u>

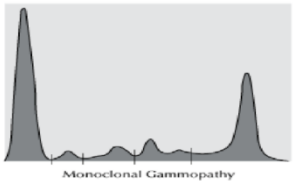
Each plasma cell produces only one type of immunoglobulin and according to the light chain the immunoglobulin can be kappa or Lambda .

Increase in gamma globulins means increase in plasma cells
Plasma cells increase in infections, inflammations and cancer .

- In infections and inflammations >> increase in all types of γ globulins >> polyclonal .

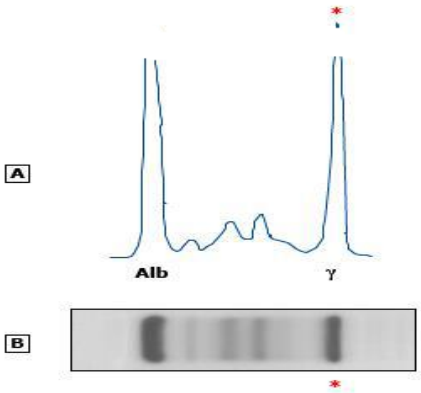


- In cancer, increase in one type of immunoglobulins that means proliferation and division of one type of plasma cells,for example if the mother cell produces IgG kappa >>all plasma cells from this mother cell will produce IgG kappa >>monoclonal .

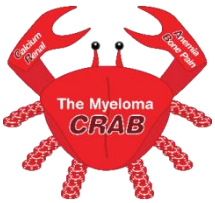


If there is a spike >> monoclony >> one type of plasma cells monoclonal increase >> one type of immunoglobulins >> these immunoglobulins are called paraproteins or M proteins.
And we call the spike (M spike) or (church spike).

To confirm that there is a spike we need to do immunofixation.(B)



As you can see there is a concentrated gamma globulins **band** and according to control bands we will know which type is increased and if it is kappa or lambda .



Diagnostic criteria of multiple myeloma : ⟶

1- Presence of serum monoclonal proteins.
2- Increase plasma cells in bone marrow or outside bone marrow - more than 50%
if the plasma cells are outside the bone marrow >> plasmacytoma
(easy to differentiate plasma cells under microscope) .
3- In organ damage :Must have two or more of these **CRAB**
-Increase in Ca++ - Renalfailure - anemia
-lytic bone lesions in long bones or in the skull (punch out lesions) Calcium elevation
Renal impairment Anemia Bone lesions

*If the patient fills(✔)all the criteria >> **multiple myeloma**
*If the patient has monoclonal increase and increase in plasma cell less than 10% & does not have CRAB >>**Monoclonal gammopathy of undetermined significance**- **MGUS**
-in MGUS we don't treat just following up (to make sure there is no CRAB).

- 1% or 2% of patients with monoclonal gammopathy with follow up MGUS will transform into multiple myeloma.
- after 25 years of following up - 40% of these patients>>MGUS will transform into multiple myeloma but 60% of these patients don't develop multiple myeloma .

--that means not every multiple myeloma starts with monoclonal gammopathy of undetermined significant).

CASE-2

Elderly with loss of balance

A 68-year-old man is evaluated for loss of balance and paresthesia (numbness) of the hands and feet of 8 months' duration.
Past History:
Type 2 diabetes mellitus: 23 years
Social History:
Drinks three cans of beer daily. (Don't hesitate to ask the patient about alcohol history)

Physical examination: (**not required**)
Short-term memory loss.
No stigmata of chronic liver disease. o Absence of vibration and proprioception in the toes and ankles

The Romberg test becomes positive when the patient closes his eyes.

Case-2

Laboratory Studies:

Hb : 9.7 >>> anemia

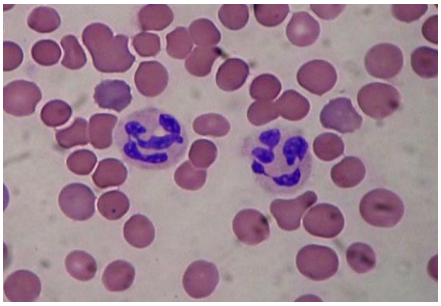
MCV : 105 >>> macrocytosis

WBC : 8500/ µL

Platelets : 250,000/µl

A peripheral blood smear is shown

Blood film



as you can see the neutrophils are hyper segmented (normally segments

are up to 5) >>megaloblastic anemia due to <u>B12 deficiency</u> or <u>folate deficiency</u>.

Megaloblastic anemia : macrocytosis and hyper segmented neutrophils.

B12 absorption needs intrinsic factor and acidity of stomach.

Causes of B12 deficiency:

Lack of intrinsic factor is most commonly due to an autoimmune attack on the cells that create it in the stomach It can also occur following the surgical removal of part of the stomach or intestines or from an inherited disorder . Other causes of low vitamin B12 include not enough dietary intake (such as in a vegan diet), celiac disease. Pancreatitis can cause B12 deficiency .

Two main drugs cause B12 deficiency: (**important**)

- <u>proton pump inhibitors (omeprazole ,pantoprazole ,…..)</u>
- <u>metformin</u>

Causes of folate deficiency :

Alcoholism substance abuse , more cooked food(lose of folic acid), celiac disease ,inflammatory bowel disease

main cause >>increase demand (young pregnant female) they must take folate supplement FeFol (Fe- iron ,Fol- folate)

Causes of macrocytosis:

Alcoholism , liver diseases , hypothyroidism, megaloblastic anemia, hemolytic anemia (the bone marrow trying to compensate so it produces premature RBCs which are typically huge

(reticulocytosis), and the machine takes the average of their size so MCV is high (artificially)), chemotherapy drugs .

---- 0-23 min

Case-3:

A 62-year-old male with anemia presented to his internist with:

-Progressive shortness of breath

-Generalized weakness

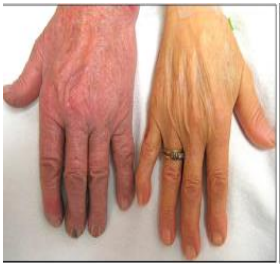
→A patient presenting these symptoms usually has anemia.

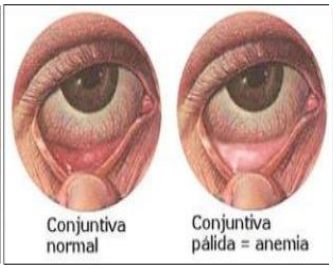
His physical exam:

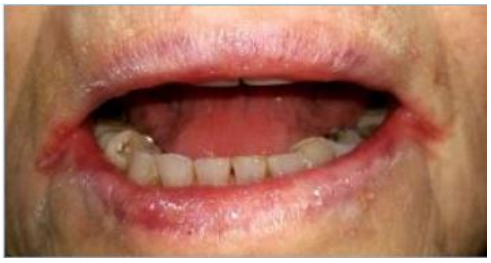
-Pale→ Pale hands; pallor in conjunctiva

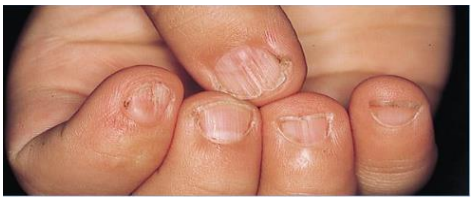
-Nail changes→ secondary to iron-deficiency anemia, nails become brittle and distorted

-Mouth→ Those with iron deficiency anemia suffer from angular cheilitis or angular stomatitis.









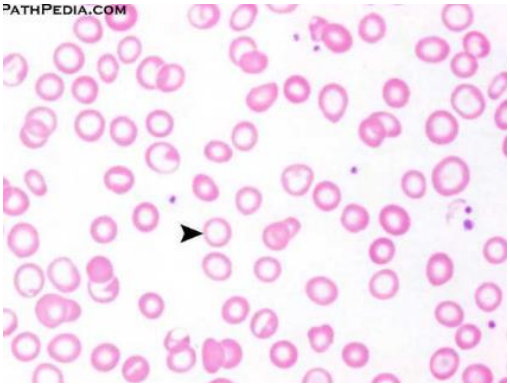
-CBC should also be checked (in the case mentioned):

HBG→ low [9.7 L]

MCV→ low [69.7 L]

RDW (red blood cell distribution width)→ high [18.4]

-The blood film for this patient→ the center of the red blood cells appears pale (central pallor).



-Iron studies for the patient:

→ Serum Iron (Fe): low [10 micro gram/ dl]

→Serum Ferritin: Low [2 ng/ml]

→TIBC (total binding iron capacity): high [450 micro gram/ dl]

Please keep in mind two important things:

1- Iron deficiency anemia is not by itself a diagnosis. There should be an underlying disease which has resulted in iron deficiency anemia. For example, elderly patients who present with iron deficiency anemia almost always actually have gastric cancer or colon cancer. The patient might be suffering from hemorrhoids.
2- Iron is very important constituent of many enzymes in the body. For this reason, iron deficient adolescents usually have weak educational achievement.

*Pregnant females need a lot more iron compared to other people. They are usually given iron supplements, but even when iron supplements are given, the level of hemoglobin does not change. That is due to iron supplements being extremely difficult to take as they cause side effects such as abdominal pain and constipation, so patients usually would only take the supplements for one or two weeks then stop.

Typically, we give oral iron until we correct the anemia for about six months so the iron stores in the body would be replenished again.

Compliance of patients to taking the supplements, wrong diagnosis, and combined immunodeficiency are problems affecting effectivity of iron supplements [no response to drug]→ sometimes, intravenous iron is given in such cases.

Case-4

A 40-year-old woman presented with one-week history of fever and confusion.

Physical examination:

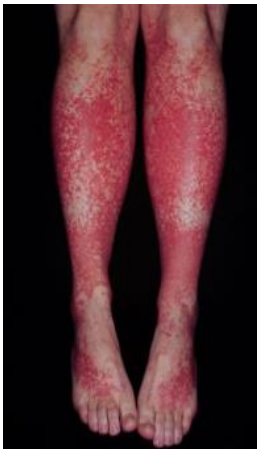
Temperature→ high [38.2]
Pulse→ 100/ min
Respiratory rate→ 20/ minute
Blood pressure→ 100/60 mmHg

Laboratory studies showed:

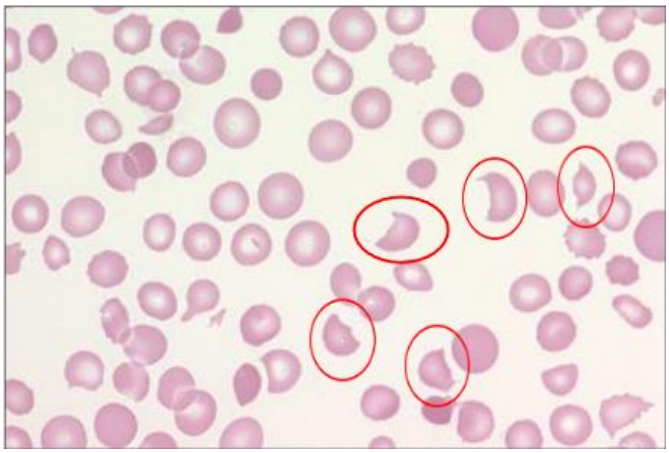
- Blood urea nitrogen: 52 mg/dL (high)
- Creatinine: 5.3 mg/dl (high)
- Hb: 12.2 g/dl (normal)
- MCV: 93 Fl (normal)
- Platelet count: 19 000/ microliter (very low)
- WBC: 8 000/ microliter (normal)

So, the patient suffers from confusion, fever, renal failure (indicated by the blood urea nitrogen test and creatinine test), and low platelet count.

Because of low platelets, she suffers from petechial rash.



The blood smear shows schistocytes [fragmented blood cells].



So, whenever a patient has a low platelet count (thrombocytopenia) and schistocytes appearing in the blood smear, the patient is suffering from a very dangerous condition—a clinical emergency.
If there is thrombocytopenia and fragmentation of red blood cells, the patient is suffering from **microangiopathic hemolytic anemia (MAHA).** One of the causes of MAHA is thrombotic thrombocytopenic purpura (TTP).
Patients with TTP usually present with MAHA, thrombocytopenia, renal impairment, neurological abnormalities (eg. Confusion), and high fever.

However, if children presented with such symptoms, they would most likely be suffering from **hemolytic uremic syndrome** [instead of TTP].

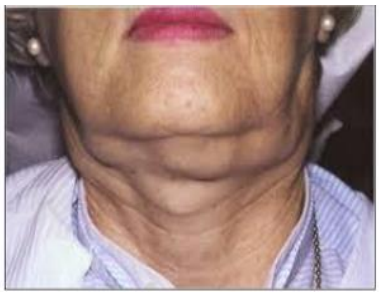
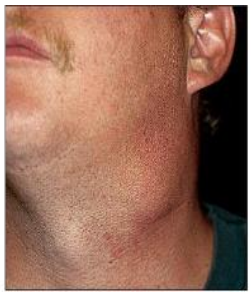
In other words, the most likely diagnosis of a patient suffering from low platelet count and schistocytes is TTP. Other differential diagnosis would be disseminated intravascular coagulation (DIC) or HELLP syndrome.
Treatment for TTP patients should be very quick since TTP is a medical emergency. TTP patient undergo plasma exchange through removing their own plasma and giving them normal plasma in return.
If the TTP patient does not receive plasma exchange, they would suffer from thrombosis, ischemia, MI, and eventually death (they can easily die).

To confirm the diagnosis of TTP, a blood test is done. The test is called the **ADAMTS13** test, which contains von Willebrand factor-cleaving protease. Because the test is done overseas, it takes about 14 days for the results to appear, so the physician should not wait and should give the treatment because TTP is a medical emergency.

Case-5:

A 45-year-old man is found to have an elevated WBC count while being worked up in a preoperative clinic for a hernia repair.
The patient apparently suffers from no symptoms: no fever, no night sweats, no fatigue, not shortness of breath.
-Past history of the patient: Mild hypertension.
-Physical examination:
→ "Shotty" adenopathy [shotty= hard and round; an old term (source: medicinenet)]
→Inguinal hernia

-His spleen is not palpable.

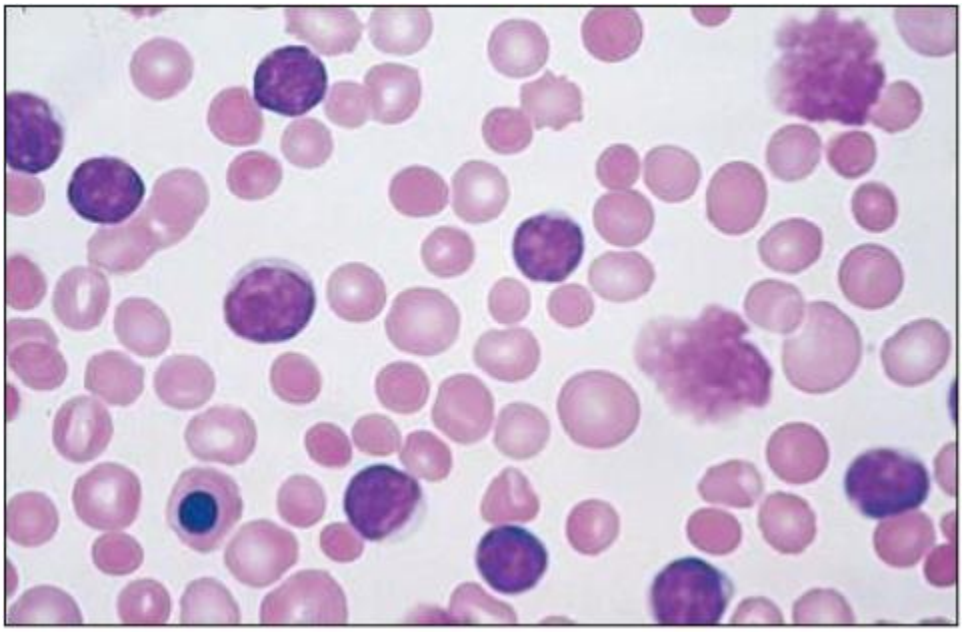
How to examine lymph nodes:

Laboratory studies:
-Hemoglobin→ 14 g/dl [normal]
-WBC: 22.0 x 10^9/ L→ 75% of which are lymphocytes
*High white blood cell count, with high percentage of lymphocytes specifically [normal percentage of lymphocytes should be 25%].
-Platelets: 203 x 10^9/ L [normal]
- A peripheral blood smear is also conducted.
-A flow cytometric analysis is made→ monoclonal, mature B-cell population that is positive for CD5 and CD23 and negative for CD 10 has been found.

Blood film:

-Normal red blood cells are present.
-White blood cells present are mostly lymphocytes [mature, normal lymphocytes]. Their size is slightly larger than red blood cells (if they were ten times larger, they would be called lymphoblasts instead of lymphocytes). Furthermore, no cytoplasm is apparent.
-Odd cells called **smudge** cells are also apparent in the blood film. A smudge cells was previously a lymphocyte whose membrane was very fragile, rendering it susceptible to distortion and injury during the preparation of a blood film.

→Smudge cells are characteristic in **chronic lymphocytic leukemia (CLL)**. Patients with CLL tend to be asymptomatic, have high WBC count, and smudge cells apparent on the blood film.



However, to confirm the diagnosis, the physician must perform another step, as such lymphocytes could be originated from a different location. Such lymphocytes have on their surface membranes specific CD markers. So, the physician should identify such receptors or CD markers through flow cytometry.

When a patient is CD5 positive, he could be suffering from one of two possibilities:

1- CLL or SLL
2- Mantle cell lymphoma

How to differentiate?

Other CD markers should be examined. In this case, CD 23 is the marker to differentiate between the two possibilities→

- CLL→ CD 23 +ve
- Mantle cell lymphoma→ CD 23 -ve

In conclusion,

1- To confirm diagnosis of CLL, a physician must use flow cytometry→ differential diagnosis.
2- CLL patients are usually elderly, present with no symptoms (asymptomatic), and have an increased lymphocyte count.

Case-6: Young female with high aPTT

- A 36-year-old female patient was recently diagnosed with right breast cancer.

- On admission mastectomy (before the surgery typically surgeons do CBC and PT ,aPTT before surgery to know if there is abnormality), she was found to have a normal PT but her aPTT was 120 seconds(normal up to 50 seconds).

Two laboratory tests are used commonly to evaluate coagulation disorders: Prothrombin Time (PT) which measures the integrity of the extrinsic system as well as factors common to both systems and Partial Thromboplastin Time (PTT), which measures the integrity of the intrinsic system and the common components.

- On further questioning, she denied any history of bleeding including a cesarean section and three other normal deliveries.
- She had no family history of bleeding.

If the aPTT or PT or both abnormal >> coagulopathy >>> problem in coagulation cascade >>increased bleeding tendency .

Problem in coagulation cascade can be factor deficiency or antibodies against coagulation factors(inhibitors) which are found in Lupus syndrome ,rheumatoid arthritis,….

To know if the problem is factor deficiency or inhibitors we do mixing studies ,we mix the patient's plasma and normal plasma (ratio 1:1)

Factor deficiency >> PTT will be normal

Inhibitors >> normal PTT then in few seconds >>abnormal
(in our case)
1:1 mixing study:
aPTT was 48 seconds that was increased to 52 seconds after one hour of incubation)

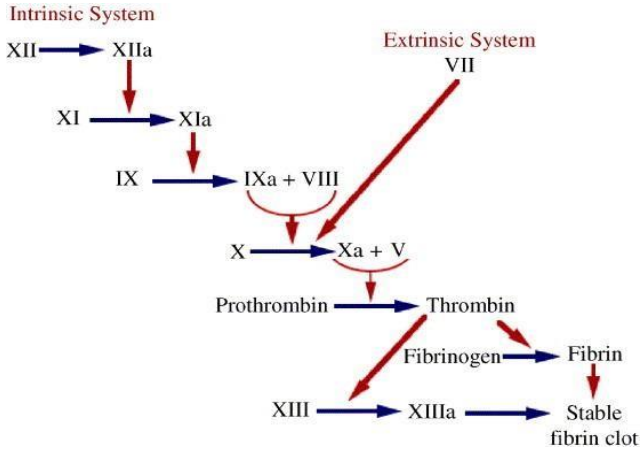
so there are antibodies against coagulation factors (inhibitors).

- intrinsic pathway factors are 8,9,11,12

  problems affect intrinsic pathway factors >> prolonged PTT

- Extrinsic pathway has only factor 7
  Problems affect it >> prolonged PT

- both intrinsic or extrinsic activate common pathway that has factors 10,5,1,2



both intrinsic or extrinsic activate factor 10 in presence of factor 5 and Ca^{++}

problems affect common pathway factors >> PTT and PT prolongation

back to our case, which factor is inhibited??

Because we have a case of prolonged PTT >> intrinsic pathway is affected

which factor 8 or 9 or 11or 12 ?

if factor 8 is inhibited >> patient has hemophilia A that is inherited and the patient bleeds a lot.

If factor 9 is inhibited >> patient has hemophilia B with family history and the bleeds a lot .

If factor 11 is inhibited >> bleeding

If factor 12 is inhibited , the intrinsic pathway can be activated by activating 8 , 9 or 11

So there is no bleeding

In our case , there is no bleeding history >> factor 12 is inhibited.

Case-7: Young male with leucocytosis

A 30-year-old man has had a progressively worsening productive cough for one month.

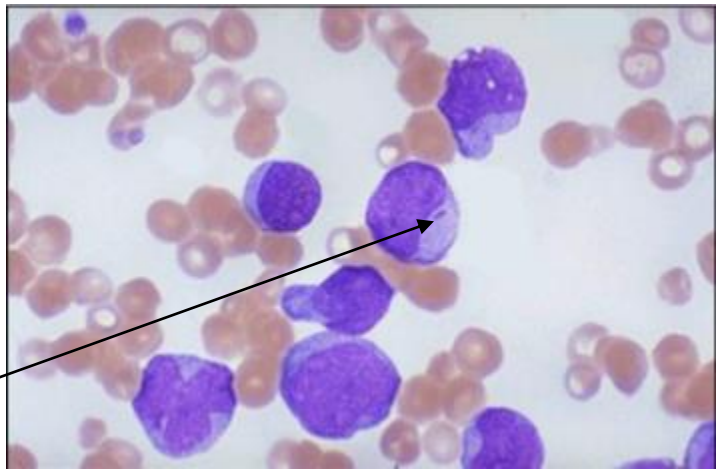
On physical examination→

- Small non-tender (not painful) lymph nodes are palpable in the axillae.
- Tip of the spleen is palpable.

Laboratory studies showed→

- Hb: 8.2 g/dl; MCV 90 fl(anaemic)
- WBC: 67 000/ microlitre (Very high)
- Platelets: 36 000/ microlitre (Low)

Peripheral blood smear:



As apparent in the blood film above, the white blood cells are really large→ Blasts.

Such blasts indicate the presence of **acute leukaemia.**

Auer rods apparent here indicates that the type of acute leukaemia presented here is **acute myelogenous leukaemia.**

So, anaemia, high WBC count, thrombocytopenia, and the presence of abnormally shaped WBCs (with very large sizes and Auer rods) all indicate the presence of acute myelogenous leukaemia.

Case-8: Young male with leucocytosis, thrombocytosis, and splenomegaly

A 41-year-old male patient presented with one-month history of:

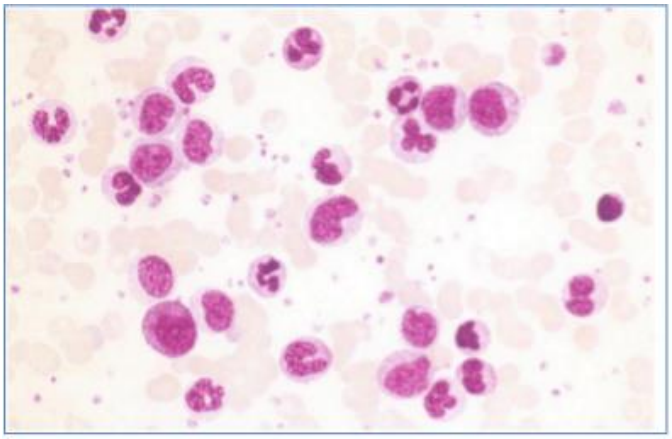
- Increasing generalised weakness and easy fatigability [indicates presence of anaemia]
- Epigastric pain but with no vomiting

-Exam was significant for splenomegaly but with no lymphadenopathy.

His initial work up→

- WBC: 78 000 [very high]
- Hb: 10.2 [low]
- Platelet count: 890 000 [extremely high]

Blood film:



In the blood film above, all kinds of white blood cells are apparent→ blasts; band cells; metamyelocytes; etc.

Usually, if patients present with splenomegaly and thrombocytosis along with the symptoms mentioned previously as well as a blood film showing all types of WBCs, they usually are diagnosed with chronic myeloid (myelogenous/ granulocytic) leukaemia [CML].

Patients with CML have a specific (9;22) translocation involving the ABL and BCR genes.

Treatment→

- Old:
  Chemotherapy
  Transplantation
- New:
- Imatinib→ works on inhibiting the BCR-ABL tyrosine kinase

Good luck

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