Hematology

Medical Committee
The University of Jorda

- Histology
- Biochemistry
- Pathology
- Pharmacology
- Physiology
- Microbiology

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lecture number : **8**

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Handout | Sheet | Slide

By: Anwer Abu Shanab

Lymphoid Neoplasms (2)

بسم الله الرحمن الرحيم

Recall that Lymphomas can be classified to 1)Non-Hodgkin lymphomas – Discussed in the previous lecture
2) Hodgkin lymphoma – which will be discussed in this lecture.

1)Hodgkin lymphoma

Basic Information

Hodgkin lymphoma is caused by the neoplastic proliferation of **Reed-Sternberg (RS) cells**, they are malignant *B-Cells* with special morphological appearance, they are:

1) giant cells
2) with 2 nuclei (actually they are one nucleus but deeply segmented in a way that can not be detected by light microscope; the interconnecting filaments are very thin that they are detected by electron microscope only) – owl-eyed nuclei-.
3) and 2 prominent nucleoli, each nucleus has a very large nucleolus in fact the nucleolus is bigger than a lymphocyte.

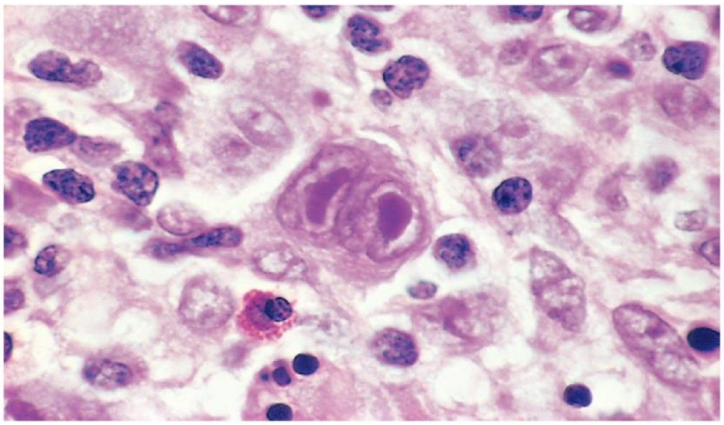

Figure 11–20 Hodgkin lymphoma—lymph node. A binucleate Reed-Sternberg cell with large, inclusion-like nucleoli and abundant cytoplasm is surrounded by lymphocytes, macrophages, and an eosinophil.
(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

- Again, RS cells are crippled, very distorted B-Cells. And the neoplasm arises from the *germinal centers* of those malignant B cells (RS cells).

-RS cells are NEGATIVE for (CD3,CD19,CD20) , POSITIVE for (CD30)
Recall that normal B-lymphocytes express's (CD19,CD20), and normal T-lymphocytes express's (CD3). – CD30 is usually expressed in very active cells like macrophages- because of that RS cells were thought to be macrophages until recently.

- EBV plays a role in the development of the disease.

Written by Mamoun Souliman

Major Differences

Hodgkin's lymphomas are a group of lymphoid neoplasms that includes many subtypes, they differ from the rest of lymphomas in the clinical and pathological manifestations.

1) They arise in a single lymph node or a chain of lymph nodes, then they spread in a **contiguous fashion** – they spread to the **closest** lymph node to the one they arose from - (stepwise spreading); in contrast to follicular lymphoma which has generalized presentation and to acute lymphocytic leukemia which manifests in bone marrow then spreads.
For example, If a patient had Hodgkin lymphoma in his cervical lymph node, when the disease progresses , it will spread to the next area which is the lymph nodes of the Chest then the axilla then abdomen then inguinal nodes…… then to the spleen, liver, and bone morrow.

2)Extranodal involvement is very rare.

3) The malignant cells are **few** in number – this is exceptional among all cancers- Normally in cancers, you have proliferation of malignant cells, and they will make up the *bulk* of the tumor, while in Hodgkin lymphoma there are only a **few** malignant cells and the *bulk* of the tumor is made up by **reactive cells** activated by RS cells.
RS cell is active and secretes *interleukins* to activate all WBC's, {lymphocytes ,eosinophils- recall that one of the causes of eosinophilia is malignancies (Hodgkin lymphoma) ,neutrophils, ……}.They accompany these cells and form the bulk of the tumor. This is a very special feature Hodgkin lymphoma. For that Hodgkin lymphoma was not thought as a lymphoma; it was known as Hodgkin disease until recently.

{The doctor compared Hodgkin to these diseases, just keep them in mind}
-Follicular lymphoma show generalized presentation. –Not localized-
-ALL manifest in the bone morrow then disseminate to the lymph nodes and solid organs –Not localized-
-Burkitt's lymphoma is seen localized in certain areas (jaw , GI system) and then it spreads like normal cancers (metastasis) . – NOT in a contiguous fashion-
-Diffuse large B cell lymphoma appears in lymph nodes and Extranodular sites (e.g., stomach) –Hodgkin's lymphoma is rarely seen in extranodular sites-

Clinical Features

They include:

1) Bimodal age distribution, which means it's more common in:

a- children , it's the **most common** type of lymphoma in **children-**

b- Elderly

(for example if we took a 100 patient sample, we'll find 40% of them are children , another 40% are among the elderly , and the remaining 20% are among different ages)

2)Presents as a painless lymphadenopathy.

3) Constitutional symptoms (B symptoms) are very common such as fever, night sweats, weight loss.

4)It spreads from the lymph node to the next area in a stepwise fashion, until finally, they reach the liver, spleen, and bone morrow.

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2)Plasma cell myeloma

Basic information

Plasma cells secretes *antibodies*, and most of them are located in the bone morrow. They have a long lifespan like B-memory cells. A plasma cell myeloma is the malignant proliferation of "long-lived" plasma cells in the bone morrow, it secretes a huge number of immunoglobulins and constitutes **10%** of all bone morrow tumors.

Most of the symptoms are related to the Immunoglobulin secretion. If we performed an immunoglobulin analysis to a normal person's serum , we'll notice that all immunoglobulins are present, but the *most common* one is IgG. And of course the immunoglobulins, are found in certain concentrations, that they don't exceed.

In myeloma there's a very large number of **one** of the immunoglobulins, again *most commonly* it is **IgG**. And the IgG's produced are identical to each other in their structure. Because they are neoplastic, they arise from a clone of malignant cells, and they have identical DNA so they will secrete **the same antibody**. That's why they are called Monoclonal Protein.**(M Protein)**

- It's an aggressive disease, and most chemotherapy and antineoplastic drugs are ineffective. Why!?

Plasma cells have a long life span and a low mitosis rate, like low grade lymphomas - basically you can't synthesize a drug to target them during mitosis- , and they are strongly associated with the stromal cells (blood vessels ,fibroblast, macrophages……) – which is protective for them from drugs.

- It's a disease of the elderly. -like chronic lymphocytic leukemia (CLL)-

- Clinically it was called multiple myeloma, "multiple: because you will have multiple bone lesions in your body" , but pathologically it's better to call it Plasma Cell Myeloma.

Pathogenesis

-Some risk factors may be present but they are only of statistical significance, they include (older age, males, black people, radiation, family history, obesity)

-There's accumulation of mutations, both at the gene level and the chromosomal level so patients will have genetic mutations and chromosomal aberrations.

-Malignant plasma cells are modestly proliferative, not like High grade lymphomas which is Highly proliferative nor are they very low. The disease is progressive and as we said resistant to chemotherapy.

- The malignant plasma cells will secrete all immunoglobulins, but most commonly they will secrete IgG. And in some rare cases they can be non-secretory.

-Normally the count of plasma cells don't exceed 3% of the total cells in the bone morrow, while in myeloma the percentage goes up to exceed 10% of the total cells of the bone morrow.

Clinical Symptoms

1. Bone pain/fractures – Neoplastic plasma cells will activate **osteoclasts** which will lead to (osteopenia, osteolysis), the bone trabeculae will become thin and the patients are more prone to **fractures**. And lytic *skeletal lesions* are seen on X-ray, especially in the skull and vertebra.

2. Hypercalcemia – It's Secondary to bone erosion {a way to think about it is when the osteoclast eat away the bone –lytic lesions- , the calcium will be pushed to the serum resulting in hypercalcemia; and it may affect the function of the heart and the nerves}.

3. Renal failure – It's Secondary to Immunoglobulin secretion, they will be produced in large amounts and they will be trapped in renal tubules producing protein cast, causing renal failure. – renal failure is very common- .

4. Amyloidosis – The free light chains aggregates/masses will circulate in the serum and deposit in tissues causing physical damage (this can damage the heart, the lungs, the kidney in addition to the protein cast).

5. Anemia – it will present itself in 2 ways: a) Malignant plasma cells inhibit normal erythropoiesis by secreting certain cytokines. b) in advanced stages, effacement of morrow due to marrow replacement by tumor cells Causing myelophthisic anemia,

-It's important to know that the anemia is present from early stages. And it's a very common clinical symptom.

6. Recurrent infections – Multifactorial, but commonly early in the disease the abnormal level of immunoglobulins *suppresses* the normal immune system, it interferes with its function and inhibits the function of normal immunoglobulins as well as normal lymphocyte. So these patients will have recurrent infection.
Also at late stages of the disease, the increase in malignant plasma cell count will cause myelophthisic anemia thus the patient will have leukopenia and he can easily develop infection.
{{{Dr. Tareq didn't mention this , I wrote it to help you better understand what's causing recurrent infections, if you find it vague or not helpful you can draw a big X over it and don't bother reading it again.}}}

"Pathoma approached this point in a slightly different manner, I will mention it here.

Recall that multiple myeloma is a malignant proliferation of plasma cells that will secrete a Monoclonal Immunoglobulin. What does that mean ?
It means that all of those malignant monoclonal plasma cells are going to secrete the **exact same antibody**, the goal of the body is to have a million different plasma cells that produces a different million antibodies. However, if you have ONE plasma cell that's producing a million antibody BUT every antibody recognize the same antigen, we will ***lose antigenic diversity.*** Which will increase the risk of infection".

7. Hyperviscosity – It's secondary to the presence of large amount of immunoglobulins, the blood will become very viscous and turbid (slowly moving). This will disrupt the circulation, and will cause symptoms in organs with fine circulation (the doctor meant by fine circulation, the organs that don't have abundant blood supply) like in:
1)The retina of the eye which will cause blurred vision.
2) some CNS related symptoms may appear. (dizziness, fatigue, focal symptoms).

Monoclonal Gammopathy of Undetermined Significance (MGUS).

This term is used when M protein is found but the other features of multiple myeloma are absent – asymptomatic patient- . It commonly progress's into multiple myeloma.

The slides mentioned that the plasma cell count should be (3-10)%

Morphology

Normal plasma cell will have eccentric nucleus, and abundant cytoplasm.

B) In plasma cell myeloma, we will notice.

1)increased plasma cells(above 10%)

2)commonly with abnormal shapes,

3) they'll become larger in size.

4) multi-nucleated.

5)prominent nucleoli.

6)immunoglobulins may appear as vacuoles in the cytoplasm and they are markedly increased in number.

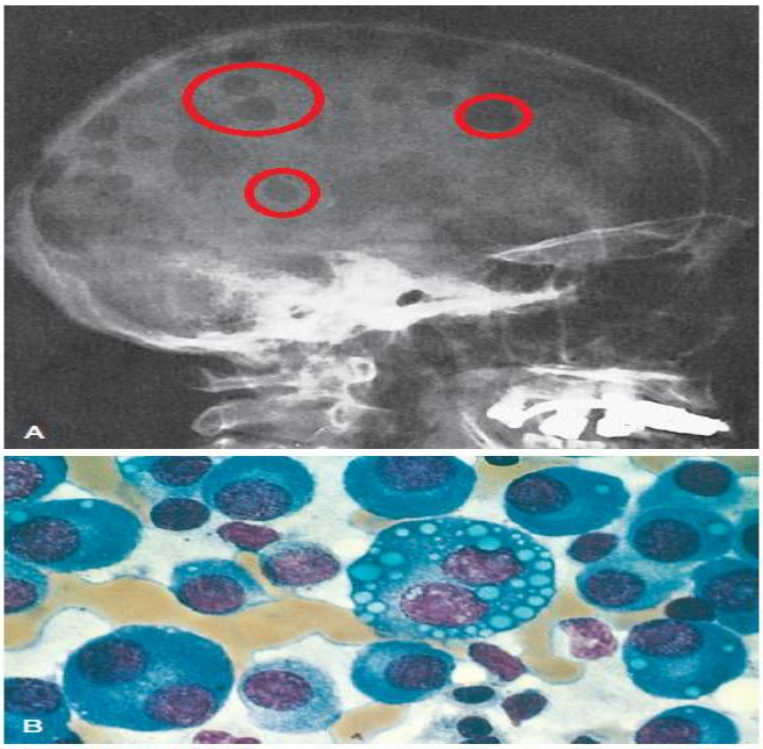
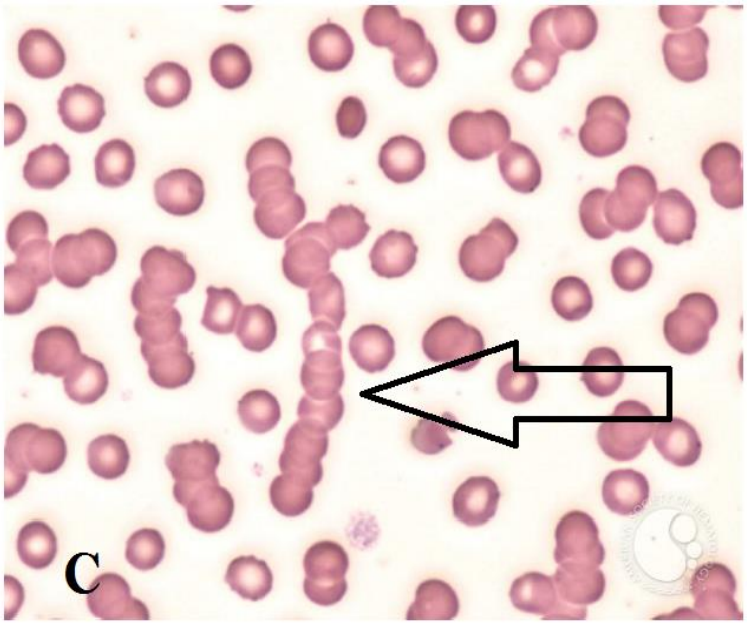


Figure 11–19 Multiple myeloma. **A,** Radiograph of the skull, lateral view. The sharply punched-out bone defects are most obvious in the calvaria. **B,** Bone marrow aspirate. Normal marrow cells are largely replaced by plasma cells, including atypical forms with multiple nuclei, prominent nucleoli, and cytoplasmic droplets containing immunoglobulin.

A) In the x-ray you can see osteolytic lesions, they appear darker in color.

C)Rouleax formation – "roo͞ lō" It's secondary to increased immunoglobulins. The RBC's accumulate behind each other, they appear as a long string of RBC's , this is not like agglutination(in agglutination we will have masses in different axis), in Rouleax they are aligned in a certain axis, a student asked if we will have high ESR and the answer is Yes.



Written by Mamoun Souliman

3)Acute myeloid leukemia

Basic information

A mutation that **inhibits** cell maturation and **activates** cell proliferation. Both of these defects results in a high number of **myeloblasts**. And the accumulation of myeloblasts in the bone morrow leads to bone morrow failure or Myelophthisic anemia.

We diagnose a patient with AML if the number of blasts **is or exceeds** 20% in bone morrow or peripheral blood. (≥ 20%)
if it was **less** than 20%, we are still in the MDS range – Refractory anemia with excessive blasts-.

Recall that:
In Myeloproliferative neoplasms we have high proliferation but good differentiation, so you can see neutrophils in the peripheral blood.
In Myelodysplastic syndrome we have abnormal maturation, the bone morrow is filled but no mature cells.
- we have both of these defects combined in AML- (the cells proliferate fast and they can not mature).

Epidemiology

it occurs at all age groups, but the incidence increases as you get older. (more common in elderly)
Incontrast with ALL (B -type- children // T-type adolescence)

Classification

AMLs are diverse in terms of *genetics*, *cellular lineage*, and *degree of maturation*. The WHO classification relies on all of these features to divide AML into four categories- mentioned later - . While the FAB classification focuses only on *Morphology*. We'll discuss both of them in more detail starting with:

A) FAB classification – French American British classification.

It's mainly based on *morphology and the degree of differentiation.* – Mx: M means myeloid-

M1: AML without maturation (blasts ≥ 80%)
Large number of blasts in the bone morrow, they are at least 80%.

M2: AML with maturation (blasts 20-80%)
Blasts are between 20-80% and the rest are neutrophils and other myeloid cells.

M3: Acute promyelocytic leukemia.– will be discussed in more detail later-
The blast went through only one step of differentiation then they stopped, it appears as **promyelocyte**. The normal count of promyelocyte is less than 8% , but here the bone morrow is filled with promyelocyte and it exceeds 20% .
Clinically those patients have severe **bleeding** , and it's life threatening, they should be treated quickly. – the doctor said that this specific type of leukemia is a classic clinical question -

M4: Acute myelomonocytic leukemia – we have both monocytes, and neutrophils , we see 20% or more blasts, 20% neutrophils , 20% monocytes.

M5: Acute monocytic leukemia – appear as purely monocytic differentiated, we have blasts and the predominant cell is the monocyte. (we don't see a lot of neutrophils)

-Note that both of M4,M5 have Monocytic differentiation but with different levels.

M6: Acute erythrocytic leukemia

M7: Acute megakaryocytic leukemia

-M6,M7 are very rare

B) WHO Classification

It is a more recent classification, it considered more factors other than the morphology, they incorporated genetics, cellular lineage, and degree of maturation.

1) AML- recurrent cytogenetic abnormality: t(15:17)-, t(8:21), inversion11

If some specific translocations were present we classify the diseases according to this translocation, and they are important because they predict outcome and guide therapy.
We should be familiar with the following:
a) t(15:17) – it causes Acute Promyelocytic leukemia (M3).
b)t(8:21) – they commonly have good prognosis.
c)inversion11 – it has bad prognosis.

if one of these translocations were present we call the leukemia after it
for example {if t(15:17) was present we'll call it –> AML-t(15:17)}

2) AML-Myelodysplasia related changes (complicates MDS) –
If there is no mutation, we will look at the *history* and the *dysplasia*. If the patient had a history of MDS and it transformed into AML(recall that MDS has a tendency to become AML) we call it → 2 //// Also recall that MDS is a chronic disease, it progresses slowly and even if it transferred into leukemia, still this leukemia will progress slowly. Not like the de novo neoplastic change.

Again, the clinical course is still **slow** m3 enha acute myeloid leukemia.

3)Therapy-related myeloid neoplasm
If there is a history of chemotherapy, which was given for other cancers, or maybe treating rheumatoid arthritis, this can damage the bone morrow causing AML, or secondary MDS, and both of them have bad prognosis.
Recall that the secondary MDS is aggressive and associated with a history of chemotherapy. The same thing in AML.

if we checked the A)cytogenetic mutations , B) history of MDS , C) history of Chemotherapy, and all of them were **negative**.
we call it (4)

4)AML- not otherwise specified
Those leukemias can be classified using the FAB classification.

Morphology – in general for AML-

There will be a lot of **myeloblasts** (above 20%) ,and they have special morphological features that include: - (A) is a lymphoblast /// (B) is a myeloblasts

1)They are large – (larger than the lymphoblast)

2)The nuclear-cytoplasmic ratio is high
(most of the cell is nucleus but we still see cytoplasm) in contrast with the lymphoblast were there's very minimal cytoplasm.
3) The chromatin is pale (not dark like the lymphoblast)
4) prominent nucleoli (2-4 nucleoli) in contrast to lymphoblast which does not have nucleoli.
5) Azurophilic Granules in the cytoplasm.
6) Auer rods, may be present- not always- in myeloblasts and they are aggregates of myeloperoxidase (if the cell after staining is positive for myeloperoxidase then this is a myeloblast not a lymphoblast) that form a needle like shape – a rod-, Auer rods are **specific** for neoplastic myeloblasts and thus a helpful diagnostic clue when present.
– Auer rod is named so after the person who described them-.
7)are seen in peripheral blood.
8) Myeloblasts express CD34 – this marker indicates immaturity, it is only present on immature cells (blasts).

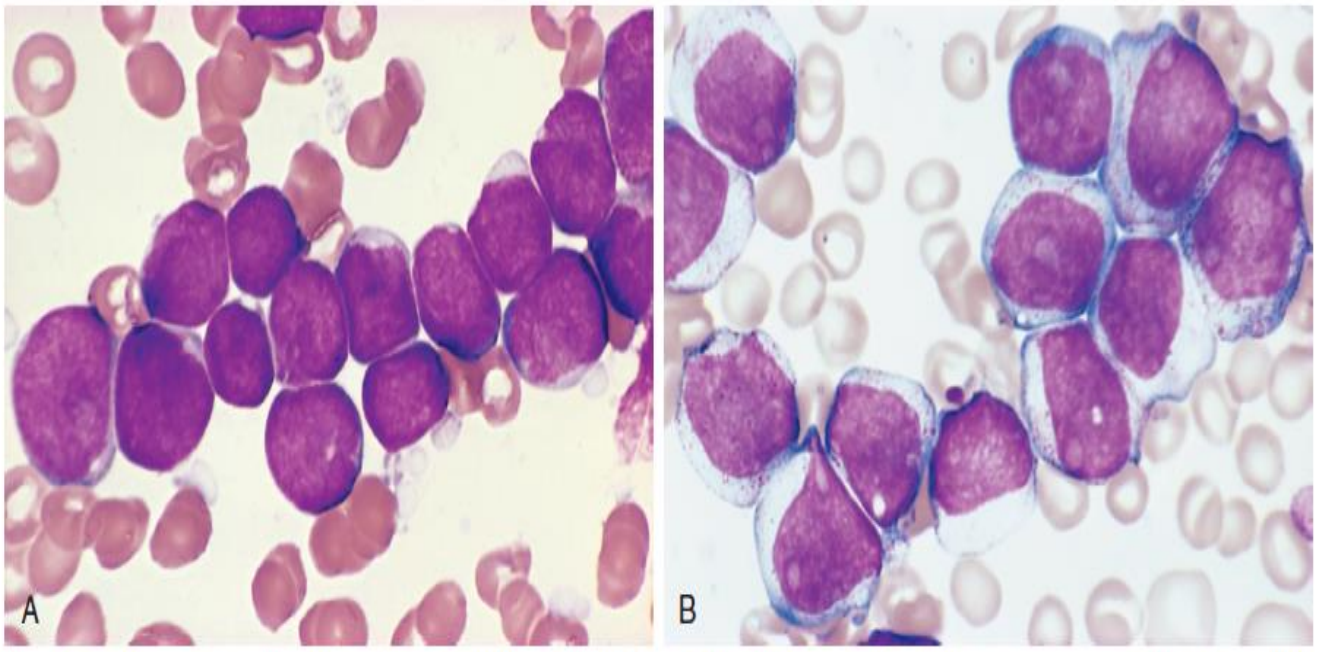


Figure 11–14 Morphologic comparison of lymphoblasts and myeloblasts. **A,** Lymphoblastic leukemia/lymphoma. Lymphoblasts have condensed nuclear chromatin, small nucleoli, and scant agranular cytoplasm. **B,** Acute myeloid leukemia. Myeloblasts have delicate nuclear chromatin, prominent nucleoli, and fine azurophilic cytoplasmic granules.
(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Now we are going to talk about 2 types of AML.

A)Acute Promyelocytic Leukemia

Basic Information

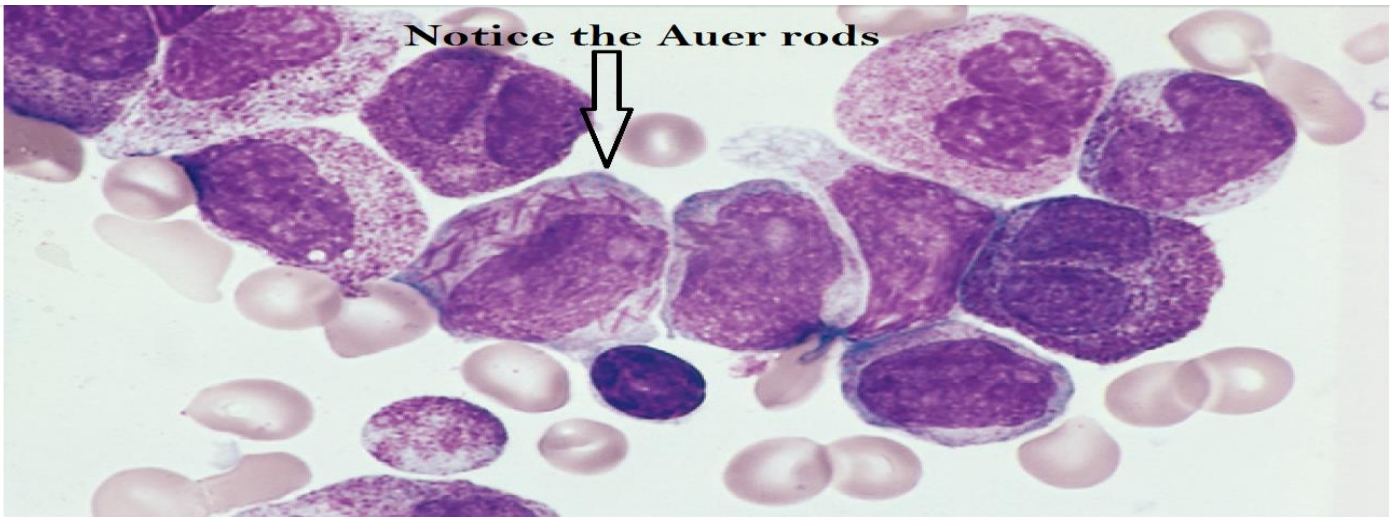
We described it in the FAB classification (M3), and in the WHO classification (AML-t(15:17)).

In acute promyelocytic leukemia , the t(15:17) translocation results in the *fusion* of the retinoic acid receptor α (RARA) gene on chromosome 17 and the PML gene on chromosome 15. Now this new protein e complex stimulates proliferation and by binding the DNA, It **blocks** cell maturation. The cells are arrested at the promyelocyte stage -cant differentiate any further- , we can reverse this blockage by giving the patient a high dose of **vitamin A.** {recall that retinoic acid is an analogue of vitamin A}.

Morphology

**Normally the promyelocyte is the largest cell between the WBC's. It has abundant granules – the most "granulated" cell between the myeloid cells-*the most granulated cell in the myeloid line is the promyelocyte*

1) it's heavily granulated.
2) Auer rods are stacked (larger in number than in myeloblasts).
3) Some cells appear with a bilobed nucleus . This doesn't happen in other AML's.



We said that these patents commonly die from bleeding, WHY?!
Because these malignant promyelocytes secrets *tissue factor*, it's a protein that activates thrombin which causes thrombosis. The blasts are circulating throughout the body so when they secrete the tissue factor, they will cause wide spread thrombosis in the body (disseminated intravascular coagulation). And we will end up with **thrombocytopenia**, as a result, the patient will have bleeding, which may cause death if not treated urgently.
- The thrombi are small and doesn't cause infarction, they only consume the platelets and clotting factors.

B) Acute Monocytic Leukemia

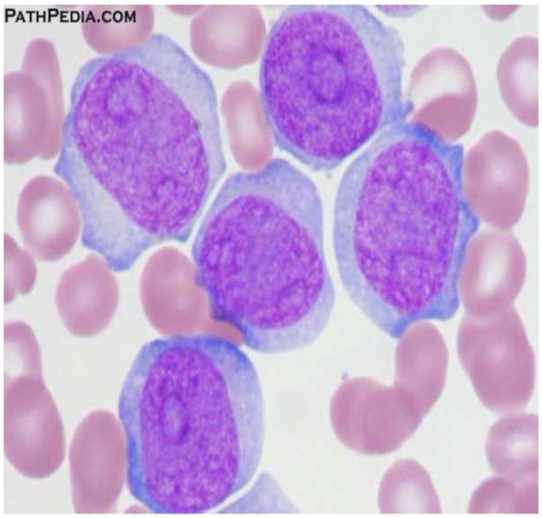
Basic Information

We described it in the FAB classification (M5), it will show as purely Monocytic – no neutrophils- , so the monocyte and its earliest stages(promonocyte + monoblast) form ≥80% of Bone Morrow cells.

Morphology: Nucleus is pale and there is prominent nucleoli**,** the monoblasts looks like the myeloblasts but differs in
1)The monoblast is **larger** than myeloblasts.

2) More abundant **agranular** cytoplasm which is slightly basophilic. – more cytoplasm than myeloblasts-.

3) The nucleus is **central** while the myeloblast's nucleus is peripheral.
4) **No** Auer rods.



They differ clinically in:
Those malignant monocytes will go outside the blood, and form **Extramedullarymasses** especially in the (skin, Gum, CNS).

A big "Thank you" to Alaa shaban for correcting this sheet :D.

Dedicated to the Beloved Harith Khalifa and The one and only Osama abu shawar.

"إذا قَلّ عَزْمي عن مدًى خوْفُ بُعده.....فأبْعَدُ شيءٍ ممكنٌ لم يَجِدْ عزْمَا" – المتنبي

دعواتكم.

These are the Major differences between NHLs and Hodgkin Lymphoma- keep them in mind for exam purposes-

	Non-Hodgkin Lymphoma	Hodgkin Lymphoma
Malignant cells	Lymphoid cells	Reed-Stenberg cells
Composition of Mass	Tumor mass consists of neoplastic **ABNORMAL** cells (lymphoid cells).	Tumor mass consists of a **Minority** of **RS** cell and the BULK is **Reactive** cells
Spread	**Non-contiguous** More frequent involvement of **Multiple Peripheral nodes**	**Contiguous** More often Localized to a **single Group of lymph nodes**
Extranodal involvement	**common**	**Not common**
Associated with	HIV	EBV

"please remember that Burkitt's lymphoma is also highly associated with EBV"

(Hodgkin Vs Non-Hodgkin):
https://www.youtube.com/watch?v=saYsSIsBObw

https://www.youtube.com/watch?v=x3c9dy3MPZo

USMLE-Style Questions:

1. A patient presents with cervical lymphadenopathy. Biopsy demonstrates a nodular lymphoma with follicle formation. This lesion would most likely be associated with which of the following?

(A) bcr-c-abl
(B) bcl-2 activation
(C) c-myc activation
(D) t(8, 14)
(E) t(9, 22)

2. A 61-year-old man has had dull, constant back pain for 3 months. He recently developed a cough productive of yellowish sputum. On physical examination there are crackles at the right lung base. A plain film radiograph of the spine reveals several 1 to 2 cm lytic lesions of the vertebral bodies. Laboratory studies show sodium 140 mmol/L, potassium 4.4 mmol/L, chloride 101 mmol/L, CO2 26 mmol/L, glucose 78 mg/dL, urea nitrogen 49 mg/dL, creatinine 5 mg/dL, total protein 8.3 g/dL, albumin 3.7 g/dL, alkaline phosphatase 176 U/L, AST 45 U/L, ALT 22 U/L, and total bilirubin 1.2 mg/dL. A sputum culture grows Streptococcus pneumoniae. Which of the following pathologic findings is most likely to be seen in a bone marrow biopsy from this man?

(A) Scattered small granulomas
(B) Nodules of small mature lymphocytes
(C) Occasional Reed-Sternberg cells
(D) Numerous plasma cells
(E) Hypercellularity with many blasts

3. A 33-year-old woman has experienced low grade fevers, night sweats, and generalized malaise for the past 2 months. On physical examination she has non-tender cervical and supraclavicular lymphadenopathy. A cervical lymph node biopsy is performed. On microscopic examination at high magnification there are occasional Reed-Sternberg cells along with large and small lymphocytes and bands of fibrosis. Which of the following is the most likely diagnosis?

a. Burkitt lymphoma
b. Hodgkin lymphoma
c. Cat scratch disease
d. Mycosis fungoides
e. Multiple myeloma

4. A 35-year-old man has had fatigue, fever, and episodes of epistaxis for the past 3 months. On physical examination his temperature is 37.4 C. Laboratory studies show Hgb 12.5 g/dL, Hct 37.6%, MCV 89 fL, platelet count 170,000/microliter, and WBC count 52,000/microliter. Examination of his peripheral blood smear shows large blasts with Auer rods. Which of the following is the most likely diagnosis?

a. Chronic myelogenous leukemia
b. Infectious mononucleosis
c. Plasma cell leukemia
d. Chronic lymphocytic leukemia
e. Acute myelogenous leukemia

5. A type of lymphoma characterized by onset in middle age and by neoplastic cells that resemble normal germinial center B lymphocyte. Additionally, it is the most common type of Non-Hodgkin lymphoma in the United States. What is the characteristic chromosomal translocation of this lymphoma?

a. T(8:14)
b. T(9:22)
c. T(11:22)
d. T(14:18)
e. T(15:17)

6. A 57-year-old man presents to his physician with a 4-month history of worsening fatigue and generalized weakness. Further questioning reveals that his clothes fit him more loosely now than they had in the past. Physical examination reveals generalized lymphadenopathy and hepatosplenomegaly. Lymph node biopsy specimens are sent to the pathologist with the presumptive diagnosis of lymphoma. Which of the following types of neoplastic cell is most common in Non-Hodgkin's lymphoma?

a. Myeloblast
b. B lymphocyte
c. Plasma cell
d. Reed-Sternberg cell
e. T lymphocyte

Answers:

1. (B) Nodular lymphomas of all types are derived from the B-cell line. The translocation t(14, 18), with bcl-2 activation, is associated with these lymphomas.
2. (D) The findings suggest multiple myeloma. He has a markedly increased level of serum globulins. The renal failure (BUN and Creatinine level) and the increased risk for encapsulated bacterial infections is typical.
3. (B) Reed-Sternberg cells are multinucleated with large nucleoli. Variants of them called lacunar cells are also seen with some forms of Hodgkin lymphoma.
4. (E) Auer rods are formed of the cytoplasmic granules of the myeloid blasts of AML and are a typical finding with AML.
5. (D) the question describes follicular lymphoma, the most common type of Non-Hodgkin lymphoma in the United States.
6. (B) Neoplastic B lymphocyte are the cells of origin in most Non-Hodgkin's lymphoma (90% of cases).

Best of luck ☺