HEMATOLOGY
&LYMPH SYSTEM

Pathology sheet

Number	6
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White Blood Cells Diseases

WBC diseases are of great importance in clinical practice. Such diseases can be neoplastic, or non-neoplastic (reactive), which are more common and can result from many causes (acute infections, steroids, …). Note that anemia and non-neoplastic WBC diseases are noticed frequently in clinical practices.

Non-neoplastic WBC diseases

These diseases can present with higher-than-normal cell count, which is called leukocytosis, or lower-than-normal cell count, which is called leukocytopenia. In some cases, the count is normal but the cells are functionally abnormal. Such cases are less common, and are not discussed in this lecture. This paradigm also applies on RBC's and platelets.

Leukocytes Normal Ranges

(Numbers and percentages are not required in the exam, because, in clinical practice, they are not so useful, and ranges are provided with the tests results. The significance of the results is really what matters. The doctor gave some examples about how the questions will be, and these are written at the end of this sheet.)

Most leukocytes in our blood are neutrophils. Next come lymphocytes, and then monocytes. Eosinophils and basophils are the least common leukocytes.

Cytopenias

As mentioned earlier, cytopenia is a case in which cell count is lower than the reference range. Sometimes, these cases can be associated with each other or with other findings. The causes, complications and treatment of cytopenias are discussed next.

Neutropenia

Neutropenia is a case in which neutrophil count is less than 1,500 cell/mm^3. When neutrophil count is less than 500 cell/mm^3, the risk of infections rises sharply. This case is called agranulocytosis.

0:00 – 10:00

Causes

The causes of neutropenia can be divided into:

- Decreased production:

1- cancer chemotherapy: chemotherapy is an aggressive treatment. During the two weeks after the chemotherapy, bone marrow specimen of the patient can show extensive fatty deposition, a morphology similar to that of aplastic anemia. This therapy and the cancer itself both compromise the patient immunity, which results in neutropenia. Those patients are isolated and are taken seriously.

2- Leukemias; which lead to the replacement of the marrow by the tumor cells.

3- Some medications may suppress neutrophils production.

4- Neoplastic proliferations: such as large granular lymphocytic (NKs or T-cells). LGL is not an aggressive tumor, but the resulting neutropenia is what kills LGL patients. (This is similar to polycythemia vera, in which the fatality

is a result of the resultant embolism and not the polycythemia itself.)

- Increased destruction:
  1- Hypersplenism.
  2- Splenomegaly also can lead to the sequestration and accelerated removal of neutrophils.
  3- Immune-mediated injury (triggered in some cases by drugs).
  4- Overwhelming bacterial or fungal infections due to increased peripheral utilization: Normally, neutrophils increase in acute bacterial infections to defend the body. But in severe cases, especially in children, the infection or the sepsis may be overwhelming and result with neutropenia.

Clinical presentation

Neutropenia increases the susceptibility to infections. Infections may occur locally (ulcers in skin, oral cavity, mucosal membranes), or generally (sepsis).

Treatment

- Antibiotics
- G-CSF (granulocyte colony stimulating factor): this factor is also given to leukemia patients receiving chemotherapy. It stimulates the production of neutrophils.

Lymphocytopenia

Lymphocytopenia is a case in which lymphocytes count is less than 1,000 cell/mm^3 in adults, and 3,000 cell/mm^3 in children.

Causes

- HIV infection (increased destruction): HIV infection results in decreased CD4+ T-helper cell count. (Note: CD34+ cells are stem cells, and mature

cells lack CD34.)

- Protein malnutrition.
- Viral infections
- Autoimmune destruction
- Certain leukemias and lymphomas
- Congenital immunodeficiency (decreased production): the previous causes are acquired. An example of congenital immunodeficiency is severe combined immunodeficiency (SCID; also known as alymphocytosis, Glanzmann–Riniker syndrome). Another syndrome is Wiscott Aldrich syndrome, manifestations can be seen, which include: lympocytopenia, thrombocytopenia with small platelets and skin eczema.

Clinical presentation

Lymphocytes are needed to fight viral infections. Lymphocytopenia results with increased risk of opportunistic infections. Such infections are caused by microorganisms that are normally present in our bodies as normal flora or in latency. Such microorganisms include: Herpes viruses (including CMV); HPV; candida fungi;aspergillus fungi and many more. Suppression of the patient immunity by any cause (including steroids intake) set them under increased risk of such infections.

Lymphocytopenia increases the risk of developing autoimmune infections (by the decreased count of T-helper cell) and malignancy (malignant cells are not "killed").

The manifestations also include those of the underlying disease. So, HIV infection leads first to lymphadenopathy (increased lymph nodes size), but as the disease progresses, lymph nodes get atrophic and become smaller in size (absent nodes). Skin eczema results in SCID case. Stigmata of pancytopenia (similar to that noticed in aplastic anemia), bleeding and anemia can also result.

Treatment

Treatment includes antifungal and antiviral intake and treating the underlying cause, according to the case.

Monocytopenia

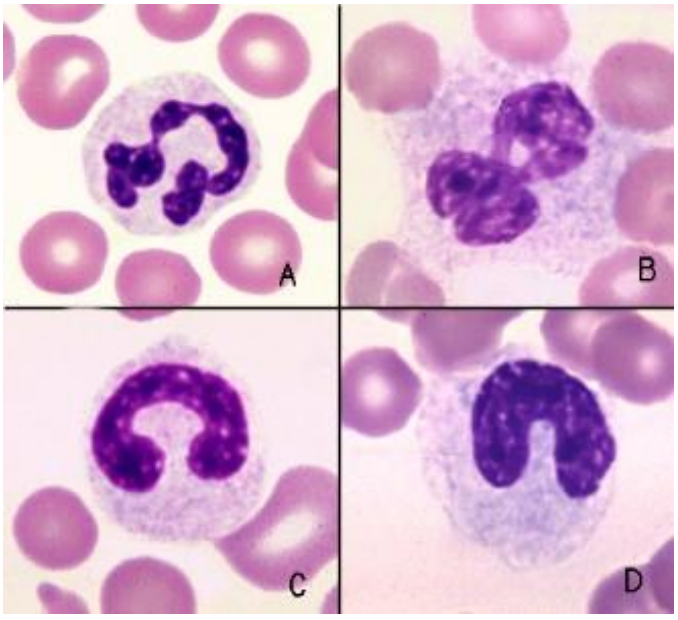
Monocyte standard count is already not that big. Monocytopenia may be present in normal people without clinical significance. Causes include hairy cell leukemia.

Low Eosinophil Count

Low eosinophil count can be found in patients who use steroids and corticosteroids. It also can be present in acute inflammations, such as acute attacks of arthritis. It is not of clinical importance.

Low Basophil Count

Basophils are normally present in low numbers. So, low basophil count is not clinically significant, though can be noticed in hypersensitivity, infections and thyrotoxicosis. No treatment is given.



Cytosis

Neutrophilia

It is present in most acute bacterial infections, in addition to sterile infections, which include

burns, myocardial infarction and trauma.

Morphological changes

These changes are called toxic changes, present in bacterial infections and denote a bad prognosis, including sepsis. So, they indicate the need of ICU isolation, or the use of more aggressive antibiotic therapy. These changes include:

- Cytoplasmic basophilia
- Large granules
- Vacuolization of the cytoplasm
- Döhle bodies

Lymphocytosis

Lymphocytosis can be noticed in virally infected patients, in whom other symptoms can be present (fever, lymphadenopathy, and splenomegaly). It also can be present with chronic bacterial infections, such as the infections of brucella and mycobacteria.

Morphology

The morphology depends of the case of the patient.

In infectious mononucleosis (EBV infection), reactive lymphocytes can be noticed. Reactive lymphocytes have abundant cytoplasm that extends around the RBC's (normally, the cytoplasm is very little). This sign is characteristic but not specific for EBV infection.

Cleaved nuclei are a sign that can be noticed in pertussis, but also in follicular lymphoma. But since pertussis usually occurs in children and follicular lymphoma occurs in older adults, overlapping should not occur.

Monocytosis

Monocytosis usually accompanies lymphocytosis, and can be noticed in the mentioned settings of lymphocytosis. It also can occur with inflammatory bowel disease, SLE and some leukemia cases.

Eosinophilia

This can occur in allergies, in hypersensitivity reactions, in parasitic infections and in asthma cases. It also can be noted in collagen vascular disease, and after taking some medications. Transient eosinophilia is noticed in atheroembolism (like pulmonary embolism).

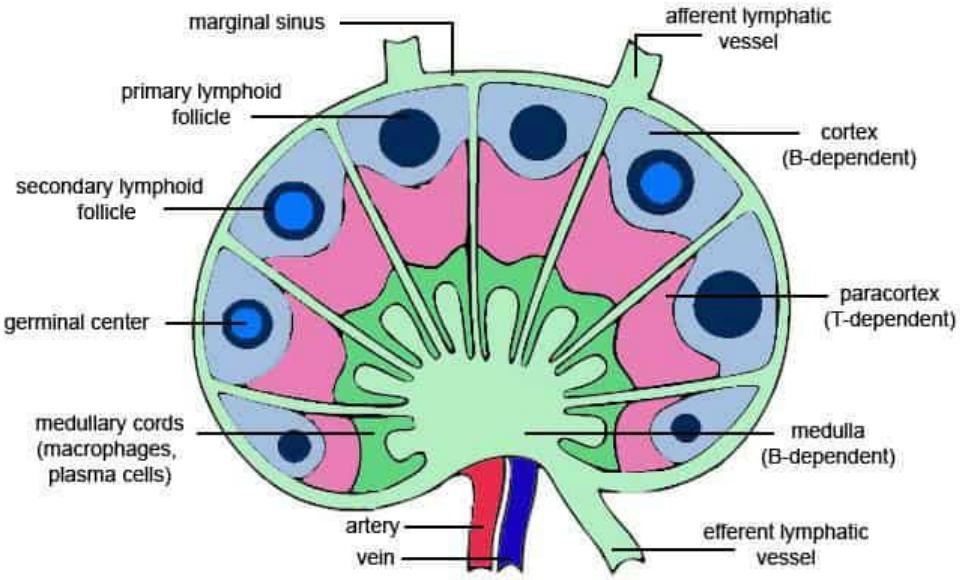
Basophilia is rare and it can be significant in chronic myelogenous leukemia.

Clinical example: if an 18-year-old patient has found to have neutrophilia, then the most likely thing they might have is an infection. But when an old patient is found to have neutropenia, thrombocytopenia and anemia, then the reason behind that is likely to be in the bone marrow (leukemia, metastatic cancer or other things).

20:00 – 30:00

Lymph Nodes Diseases

Histology of lymph nodes:



Lymph nodes function in the filtration of infections and offenses.

Lymph nodes have two major sites:

- The cortex: rich with B-cells.
- Paracortex: rich with T-cells.

Sinuses are modified vessels, through which pass antigens and proteins.

Reactive Lymphadenitis

Lymphocytes respond to antigen stimulus in the body (Infections, autoimmune). This leads to lymph node enlargement (lymphadenopathy). The infections causing lymphadenitis are varied and numerous, and may be acute or chronic.

Acute Nonspecific Lymphadenitis

It follows bacterial or viral infections. It can be localized (hand infection; sore throat), or generalized (sepsis or generalized viral infections). Acute lymphadenitis is commonly painful, which is very important sign that is not present in lymphomas.

Histologically, follicles are larger, and filled with germinal center macrophages. Sinuses enlargement is also seen with multiple histiocytes. The most important sign is the presence of neutrophils, which is not noticed in chronic lymphadenitis.neutrophils can be in small amounts in the paracortical space, or they may form abscess.

Chronic Nonspecific Lymphadenitis

This can be divided into:

- Follicular hyperplasia: proliferation of the germinal center B-cells, resulting in enlarged follicles. This form of lymphadenitis can be confused morphologically with follicular lymphoma. Findings that favor follicular hyperplasia are: the preservation of the lymph node architecture (the distinction between cortex and paracortex is easy); variation in the shape and size of the germinal centers; the presence of a mixture of germinal center lymphocytes of varying shape and size; the younger age (old adults are more likely to have lymphoma); negative BCL2 stain (follicular lymphoma is BCL2 positive).

- Paracortical (diffuse) hyperplasia: proliferation of T-cells in the interfollicular areas. This can be encountered in viral infections (such as EBV), after certain vaccinations (smallpox), and in immune reactions induced by drugs (especially phenytoin, which also can cause folate deficiency and megaloblastic anemia).

Sinus Histiocytosis

In this case, the lymph node gets larger, and the sinuses get filled with macrophages and histiocytes. This case should raise the suspicion of metastatic carcinoma. For example, if a breast cancer patient had enlarged axillary lymph node, then this can be caused by metastatic malignant cells, or by obstruction.

Revision Questions

1- Which one of the following is not one of the neutrophil toxic changes?
   a. Döhle bodies
   b. Cytoplasmic vacuolation
   c. Cytoplasmic basophilia
   d. Cytoplasmic granulation
   e. Nuclear hypersegmentation

2- Large granular lymphoma is associated with:
   a. Neutropenia
   b. Lymphocytopenia
   c. Basophilia
   d. Neutrophilia
   e. Eosinophilia

3- Monocytopenia is associated with:
   a. Chronic lymphocytic leukemia
   b. Large granular lymphoma
   c. hairy cell leukemia
   d. Hodgkin lymphoma
   e. Lymphoplasmacytic lymphoma

   Note: LPL is the only tumor that is associated with cold IgM antibodies (macro in the name). CLL, however, is associated with warm antibodies.

4- What is the characteristic finding that lymphocytes have in peripheral blood in patients with pertussis?
   a. reactive lymphocytes
   b. Lymphocytes with cleaved nuclei
   c. Normal lymphocytes
   d. Chromatin nucleoli

e. Hairy cytoplasmic extensions

Answers:

1	2	3	4
e	a	c	B

Note: neutrophil hypersegmentation is associated with megaloblastic anemia.

Some questions that were mentioned in the lecture:

- A Patient (75 years) with colon cancer presents with Hb concentration of 10g/dl (normal = 13-15 g/dl), fecal blood test was positive, which one of the following finding is consistent with this case?
  a. Low iron total binding capacity
  b. High hepcidin
  c. Low ferritin
  d. Normal MCV

  the patient has iron deficiency anemia; so the answer is c.

- A young female who suffers from shortness of breath, has high levels of LDH, low levels of haptoglobin splenomegaly and high hemoglobin levels: this is a case of autoimmune hemolytic anemia
  it may be associated with B cell lymphoma.

The End