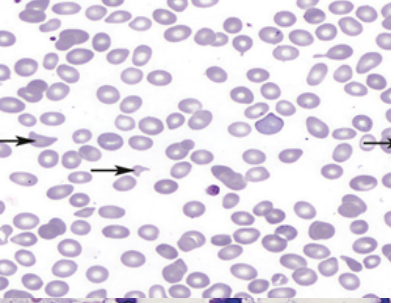

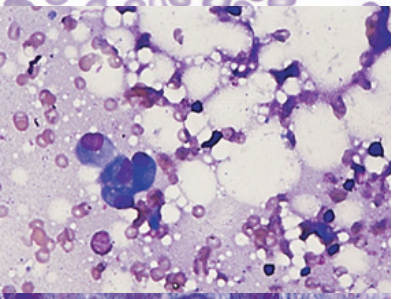

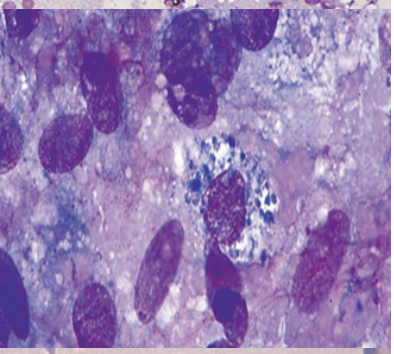

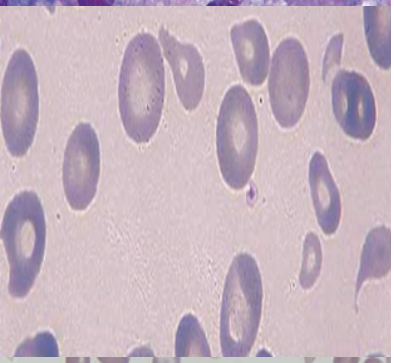

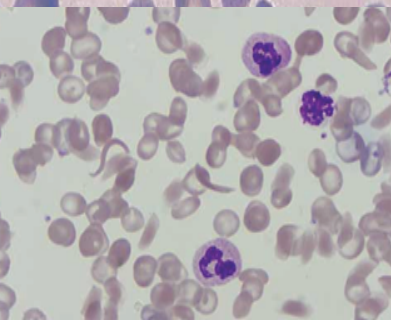

HISTOPATHOLOGICAL RESEARCH TECHNIQUES OF BLOOD TISSUE

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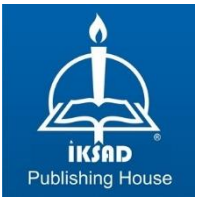

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PREFACE

As the living structure grows and becomes more complex, essential substances for the body cannot be taken only by contact, they are taken into the body by different systems and then transported to the necessary areas. The evolution of blood is thought to have originated from seawater. Inside; water residues, molten salts, nutrients, etc. Compositions containing blood plasma have a structure similar to sea water. In the plasma liquid, performing various functions; present as blood cells, proteins, ions. It carries out the process of transport with blood, cells and external environment and contributes to the formation of the internal environment. blood cells; red blood cells, white blood cells and platelets. Many histological techniques are used in blood perperate smears. However, many techniques related to diseases are used and their histopathology is evaluated clinically. The most commonly used histological stains in histopathology are Hemotoxylin, Wright-Giemsa, Giemsa and Diff-Quik stains. They are important in the diagnosis and evaluation of many diseases. In addition, electron microscopy is used

in histopathological conditions. Thus, blood has an important place for a living organism to survive, and it is a major factor in preventing many diseases thanks to the techniques used. Especially in the diagnosis and treatment of vital signs of living organisms, the techniques and uses of these blood samples, which are applied today, are of great importance and should be supported by necessary studies.

CONTENTS

PREFACE i
CONTENTS iii
INTRODUCTION 5
Peripheral Smear Evaluation 7
Routine Paints 15
Aplastic Anemia 25
Iron Deficiency Anemia 26
HbH Disease 28
Megaloblastic Anemias 32
Sickle Cell Anemia 36
Polycythemia Vera 38
Malaria 40
Acute Lymphoblastic Leukemia 57
Acute Myeloblastic Leukemias 59
Hairy Cell Leukemia 60
Plasma Cell Diseases 62
Lymphocyte 67
MONOCYTE 68
Basophil 72
Eosinophil 73
Amegakaryocytic Thrombocytopenia 76

Glanzman's Thrombasthenia 77

Chronic Idiopathic Thrombocytopenic Purpura 78

Duties of Blood.....84

CONCLUSION.....86

REFERENCES 87

INTRODUCTION

As the living structure grows and becomes more complex, essential substances for the body cannot be taken only by contact, they are taken into the body by different systems and then transported to the necessary areas. The evolution of blood is thought to have originated from seawater. Inside; water residues, molten salts, nutrients, etc. Compositions containing blood plasma have a structure similar to sea water. In the plasma liquid, performing various functions; present as blood cells, proteins, ions. It carries out the process of transport with blood, cells and external environment and contributes to the formation of the internal environment. blood cells; red blood cells, white blood cells and platelets.

Blood Cells

1) Red Cells (erythrocyte/RBC)

2) White Cells (leukocytes/WBC)

- Granulocyte

-Neutrophil

-Eosinophil Polymorphic

-Basophile

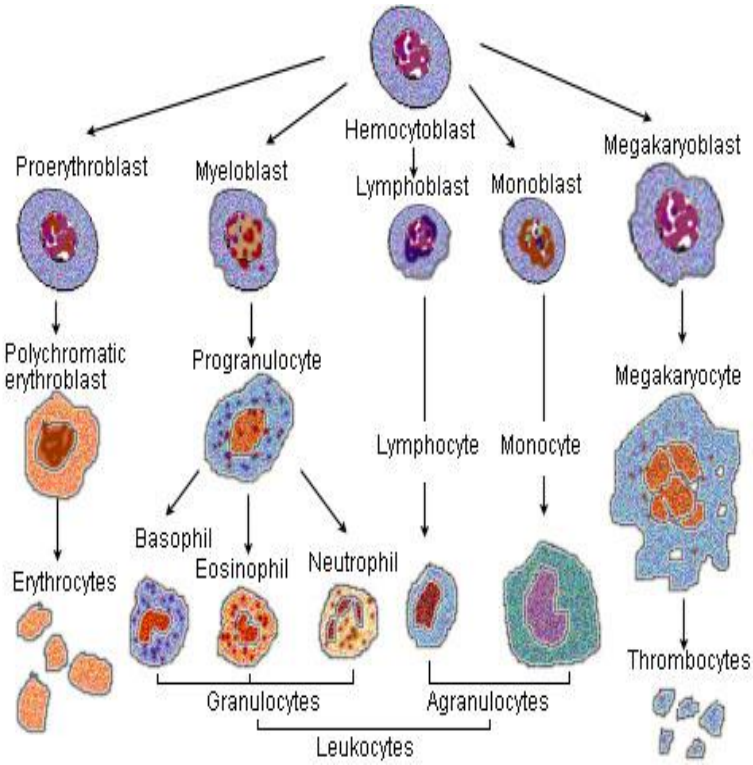
-Agranulocyte

-Lymphocyte

-Monocyte Monomorphic

-Plasma Cells

3) Blood Platelets (platelet/platelet/Plt



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Peripheral Smear Evaluation

Separate staining of the cell nucleus and cytoplasm by spreading a drop of blood on the slide is evaluated in all three cells with Giemsa, Hemotoxylin Eosin, MayGrünwaldGiemsa, Wright. In the peripheral smear,

erythrocytes are evaluated in terms of size, morphology, dye uptake, inclusions, presence of parasites and nucleated forms and their relationship.

Staining is used to highlight important features of tissue and increase texture contrast. Hematoxylin is a basic dye commonly used in this process, which stains the nuclei giving them a bluish color. Eosin (another dye dye used in histology) stains the nucleus of the cell, giving it a pinkish stain. However, there are few other staining techniques used for specific cells and components. Staining is a medical procedure commonly used in the medical diagnosis of tumors to which a dye color is applied to locate diseased or tumor cells or other pathological cells at the posterior and anterior border of sample tissues. [1]. In biological studies, staining is used to mark nucleic acids, proteins, or gel electrophoresis to mark cells and aid microscopic examination [2]. In some cases, multiple staining methods such as various different staining, double staining or multiple staining are used. In histology, fixation refers to the use of chemicals to preserve the natural tissue structure and preserve the cell. structure

intact. Often, neutral buffered formalin is used when a light microscope must be used in this situation. can be used to run the study. Fixatives irreversibly increase the protection of tissues and cells. process via cross-linking proteins. However, while the process serves to preserve the structure of the cell, the purpose of histological studies has been found to destroy and denature proteins. Formalin fixation DNA, miRNA and mRNA tissues and extraction of these components for histology can lead to erroneous results [3]. In particular, fixation hardens the chemical composition of all tissues by dividing cells and tissues into certain sections, and ensures that they are protected by preventing deterioration. In addition, fixatives change tissue penetration and affect reproduction and antigens that may pose harmful risks. Thus, if we divide the fixatives into sections, there are two forms: The first one is perfusion and immersion of the prepared tissue. These fixatives are spread throughout the body of animals. The perfusion process progresses more slowly, increasing the time and allowing the use of a fixative in one shot [4]. There are many types of fixatives that we use. The most commonly used chemical is formaldehyde. When we look

at another type of fixative, this chemical called Neutral buffered formalin (NBF) stabilizes the amino acids found in proteins and provides a very important protection of the cell structure in the tissues. In addition to these, the paraffin-formalin chemical (paraformaldehyde-PFA) needs to be newly prepared in order to be more effective in the tissue if immunostaining is to be done. It has been shown in studies that Bouin's fixative is much more effective in tissues such as the embryo and brain, which we call small tissue, especially in sensitive and soft tissues. In addition, Bouin's fixative provides good preservation of nuclei and glycogen in cells within the tissue. However, it has disadvantages as a side effect, and it has been shown in many studies that the penetration in the tissue is slow and it degrades the mitochondria and kidney tissues. If we define dehydration briefly, its main purpose is to remove water from the tissues to be studied, to ensure its solidification and to allow us to obtain much thinner sections [4]. When we look at the embedding process, the obtained tissues must be embeded before painting. The embedding process is made by using paraffin wax, which is used to increase the extraction [1]. However, as these

fixatives are very useful, they can also have side effects, especially cell deterioration due to long-term exposure to the structures of the tissue. Especially, this negative situation causes many problems when hybridization process originating from RNA is performed. In order to eliminate this problem that may arise, burying the tissues quickly after freezing is to remove the paraffin from the environment when staining. In addition, the use of PFA fixatives offers a reliable solution to improve morphology.

Sectioning: Sectioning in histology can be defined as sectioning the tissue embedded in paraffin in a microtome device in the form of a strip with a microtome knife. In order to examine the sectioned tissue, it can be taken on the slide and the staining process can be started [5]. Thus, a large number of thin tissue sections are taken at the desired thickness and prepared by cutting with the paraffin method. Removal of Antigens: After the sections are taken, the antigens must be removed from the environment after the fixation process.

It is widely used especially in staining in histological studies, medically pathological diagnoses and forensic

researches and provides many benefits. If we make a histological study, we can divide this staining process into five. When we examine these stages, they are fixation, processing, embedding, splitting and staining. Long ago, histologists used ready-made chemicals to microscopically examine the tissues they wanted. These chemicals, especially used in studies, were potassium dichromate, alcohol, and mercury chloride. These fixatives and dyeing agents were the most advanced. Shortly after, new colored dyeing agents that could be used in dyeing techniques we still use in the laboratory today were developed and started to be actively used in studies. These painting techniques used today; carmine, silver nitrate, Giemsa, Trichrome Stains, Gram Stain, and Hematoxylin, among others. With the development of chemical methods, there have been great changes in the techniques used in histological staining for studies. In particular, the processes used and performed in molecular biology experiments and immunological techniques represent histochemistry and provide significant convenience in the examination of organs and tissues. Hematoxylin is the most widely used basic dye, especially

in tissue examinations. In the cell, the nucleus processes and dyes it, giving it a bluish color, while eosin gives the nucleus a pinkish color [6]. These changes in dyeing techniques and dyes are still used, and new, more recent dyeing techniques have been introduced to replace them [7]. Due to the medical proof of the chemicals currently used in dyeing, the dyeing variants used in the past are no longer used. However, this greatly reduces the human workload due to the developed dyeing techniques. Many case studies in histology show that a combination of different staining techniques is used in today's histology. Dyeing is of great importance in order to obtain good results in the studies. In order to provide a histological improvement in modern histology and to provide a better understanding of the tissues and cells to be examined, various dyes have been developed and combined with other dyes.

Simple Giemsa Painting:

- Preparation of preparations.

- Fixed in methanol".

- The dried preparation giemsa dye is applied (30 minutes-Giemsa dye is diluted 1:20 with distilled water).

- The preparation is cleaned with distilled water.

- The prepared preparation is examined under a microscope at 40X magnification.

Note: If the preparations are to be stored, the mineral oil on them should be washed.

The key to quality painting is the appropriate time and use of the correct fixative solution. Cellularly paints 3 contents:

- Core

- Cytoplasm and its contents

- Intercellular matrix: myxoid matrix, necrotic structure, fibrin and keratin

Dyeing methods can basically be examined in 3 groups:

1- Routine dyes (PAP, H&E, Giemsa, Diff-Quick, Toluidine Blue)

2- Cytochemical staining (PAS, Musikarmen, AB, Congo Red, Fontana silver stain) (For microorganisms: Gram, Ziehl Neelsen (tbc), Gomori methenamine silver (Pneumocystis carini, fungus)

3- Immunocytochemical staining

Routine Paints

Nuclear dyes: Hematoxylin: Harris, Mayer, Gill (nuclear dye in PAP and H&E dye)

Cytoplasm stains: Eosin: Eosin-Alcohol (EA) in H&E: In PAP stain, there are 3 types: EA-36, EA-50, EA-65

Orange G (OG 6) : In PAP stain Intercellular matrix and other ground dyes: May-Gruenwald-Giemsa (MGG)

Wright-Giemsa, Giemsa Diff-Quik These are usually Romanowski type paints.

Routine Staining with Alcohol Detection: Before the smear dries, dye should be applied to non-gynecological cytology for at least 15 minutes after fixation in 95% ethanol (equivalent fixative solutions: 100% methanol, 80% isopropyl alcohol or propanol). Carnoy's solution is used for erythrocyte hemolysis in liquids with high blood volume (60 ml of 95% ethanol + 30 ml of chloroform + 10 ml of glyceal acetic acid containing solution for 3-5 minutes and when it becomes colorless, 95% alcohol is determined). Papanicolaou stain (PAP) is the most preferred method in gynecological and non-gynecological cytological smears. PAP is the basic staining method for SVS and is frequently preferred for all other cytological material types. Hematoxylin & Eosin (H&E) is used in FNAC materials and other non-gynecological cytological materials. Hematoxylin in PAP and H&E is basic and binds to nucleic acids in the nucleus and provides staining. In H&E, the nuclei are stained blue-violet to violet. Eosin is an acid aniline dye. It binds to basic or negatively charged structures (cationic amino groups in proteins) and causes it to turn pink. Harris, Mayer's and Gill hematoxylin are used as hematoxylin. Intense nuclear

staining may occur with Harris hematoxylin. In Mayer's and Gill hematoxylin, the time is longer, but there is no such risk. The cytoplasmic dyes used in PAP are Orange G (OG 6) and Eosin Alcohol (EA). They are acidic and stain the cytoplasm a bright dark orange color. All varieties of EA can be used in many propagation. In addition, cytochemistry and immunocytochemistry dyes are also used in smears fixed with alcohol.

Routine Staining in Air-Dried Preparations: Contains Romanowski variety dyes (May Grünwald Gieamsa: MGG, Giemsa, Diff-Quik), methylene blue and eosin. The acidic component of the cell (cytoplasm and chromatin) binds with the basic content of the dye, methylene blue, resulting in a blue color unique to Giemsa dye. It is useful in detecting hematological cells (bone marrow and lymph node cells), colloid, mucin and intercellular matrix structures (metachromatic staining of chondromyxoid matrix structure in pleomorphic adenoma, basal membrane-like hyaline substance in adenoid cystic carcinoma). In addition to PAP or H&E staining, Giemsa staining is also necessary in the FNAC of the lymph node,

salivary gland and thyroid. The advantage of these paints is that they can be applied easily and quickly. However, the smears must dry quickly in order for the cells to retain their appearance. If drying is slow, artifacts increase. For this reason, methods such as shaking by hand or blowing hot can be applied. Drying time is related to the thinness of the material and its uniform distribution. Both methods have some unique advantages.

Erythrocytes (Red Blood Cells): They are round, non-nucleated red blood cells in mammals, and oval and nucleated cells in fish, frogs, reptiles and birds. They carry the hemoglobin protein and the task of hemoglobin is to bind blood gases and transport them to the required places. When we look at the history of erythrocytes, it has been accepted by many scientists that they are a passive bystander in thrombosis. In addition, clinical and epidemiological studies have demonstrated quantitative and qualitative abnormalities associated with both arterial and venous thrombosis in RBCs, including hematocrit, sickle cell disease, thalassemia, hemolytic anemia, and malaria. With the increase in studies, it has been suggested

in these studies that RBCs play an important role in thrombus formation and increase thrombus stability. The findings of the available studies suggest that RBCs may support the pathophysiology of thrombosis and may reveal potential strategies to therapeutically target RBCs to reduce thrombosis [8]. If we look at the most important feature of RBCs, they have a significant biophysical and biochemical effect, especially on platelets. First of all, RBCs affect the physical position of platelets in the vessels. In addition to its important effect especially in smooth vessels with arterial shear velocities, RBCs affect platelet margination and by promoting them, it provides a large number of enrichment of the platelet concentration near the wall [9]. If we include the abnormal size, shape or viscoelastic properties of RBCs, it has been shown in studies that many diseases involving qualitative defects are also associated with thrombosis. In particular, sickle cell disease (SCD) experiences vaso-occlusive crises and 25% of SCA patients have a stroke when we clinically evaluate the patient up to the age of 45, and 50% of them are ischemia [10]. Patients with thalassemia have an increased risk of thrombosis, especially following

splenectomy. 27 Similarly, patients with hereditary spherocytosis (HS) following splenectomy have a 7.2- and 3.3-fold increased risk of arterial thrombosis and VTE, respectively. In both cases, splenectomy may increase thrombosis by decreasing the clearance of abnormal red blood cells [11]. Thrombosis in these disorders has great effects on both erythrocyte dysfunction and other blood cells and vasculature. This width of RBC distribution is positively associated with the risk of developing ischemic stroke, as it greatly changes the volume of circulating erythrocytes [12]. Unmodified red blood cells can either bind directly to the endothelial or sub-endothelial matrix, or have the ability to bind with other blood proteins, including neutrophils and platelets, by active interaction [13]. However, studies have shown that RBCs have both biophysical and biochemical effects on platelets. The first of these, RBCs, affects the physical position of platelets in the vessels, and it has been concluded that RBCs promote platelet margination in smooth vessels with arterial shear velocities [9]. It provides simulations called in silico and increases the connection between the platelet-vessel wall of margination and reduces the distance between the

flowing platelets and the thrombus. Thus, it has been suggested in studies that this interaction significantly increases platelet aggregation in thrombus by increasing the continuity and duration of this interaction [14]. When we look at the properties of RBCs, the most important thing is that it binds fibrinogen and as a result of this interaction, it is considered as a tool that provides erythrocyte sedimentation and blood viscosity. It has also been reported that the RBC content of the thrombus is closely related to the size of the thrombus. In the studies carried out, especially the findings in in vitro and in vivo models reveal the dual but independent contributions of the crosslinking of RBCs by showing that the fibrin network density and coagulation factor XIII(a) mediated fibrin a-chain retention in the clot [15]. In addition to the differences in arterial thrombosis and VTE pathophysiology, it can be said that RBCs have a significant effect on blood viscosity, cellular function and thrombus formation, structure and stability. In line with these effects, RBCs most likely contribute significantly to arterial thrombosis and VTE. If we are to introduce these contributions, many methods are required to evaluate both

the biophysical and biochemical properties of RBCs [14]. In studies and examinations, an examination is made by using fluorescent flow cytometry in the reticulocyte channel to count the fragmented red blood cells. A specific area under the RBC population in the RET scatterplot is used to identify lysed red blood cells. Red blood cells lack nucleic acids, so the intensity of the measured fluorescent signals (SFL) will be substantially lower.

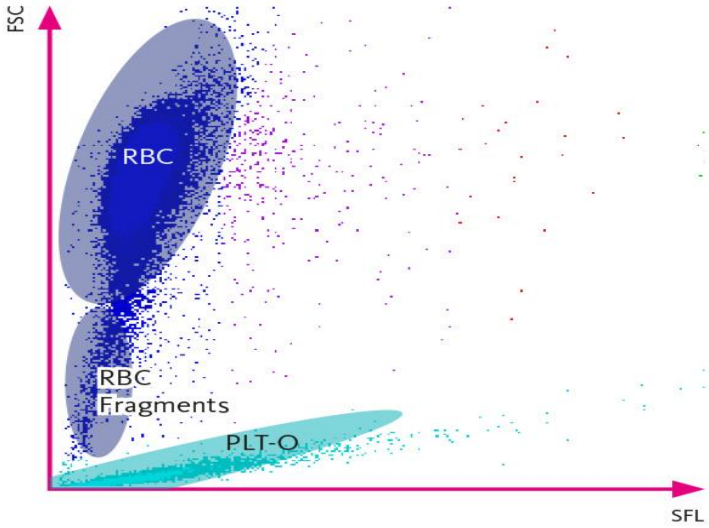


Figure 2: Each cell is plotted in a RET scatter plot based on its fluorescence intensity (SFL on the x-axis) and its

high-angle forward distribution (FSC on the y-axis), which is indicative of cell size information as well as reflecting characteristics of the cellular content. The triangle indicates the detection region of lysed red blood cells (FRC) [16]. Fragmented red blood cells are usually the result of mechanical damage. Mechanical damage is also often observed due to irregular blood flow or in contact with pathologically impaired endothelium. Another common site is the microcirculatory vessels. These abnormal shear forces damage red blood cells, creating cell remnants that appear as “helmets” (cells with two conical and horned protrusions at each end) and other strange shapes when viewed under the microscope.

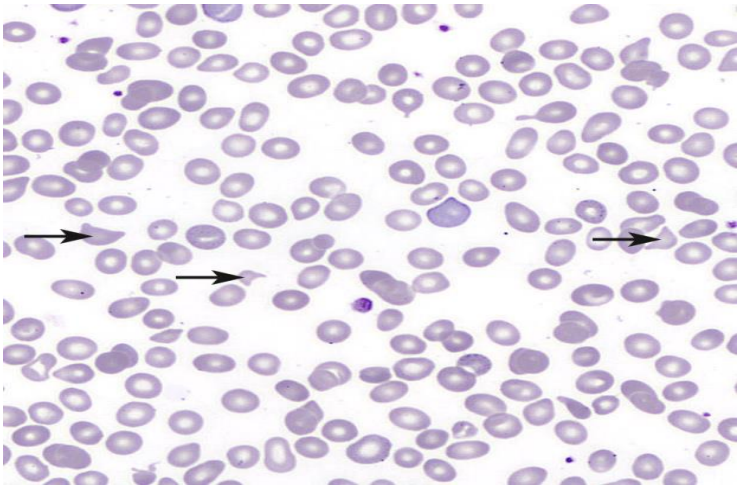


Figure 3: 'Helmet' cells (arrows) on peripheral smear-hematoxylin-eosin staining [16].

In the study, they are used as erythropoiesis stimulating agents (ESA) to better manage anemia and increase hemoglobin (HgB) level. Thus, it is claimed that it reduces the need for RBC transfusion. However, this event has been shown to increase the risk of thromboembolic events. Studies have also shown that the use of ESA in patients with cancer reduces survival, increases mortality during the active study phase, and increases the risk of cancer progression [17].

Aplastic Anemia

Its detection is made by pancytopenia in the peripheral blood and adiposity in the bone marrow. An increase in the amount of lymphocytes, plasma cells and mast cells can be observed in the bone marrow. In the peripheral smear, erythrocytes may be macrocytic with excessive secretion of erythropoietin. Bone marrow evaluation should be done by biopsy, not by aspiration. It is important for the diagnosis that less than 25% of the hematopoietic cells in the bone marrow and the remaining part are fat.

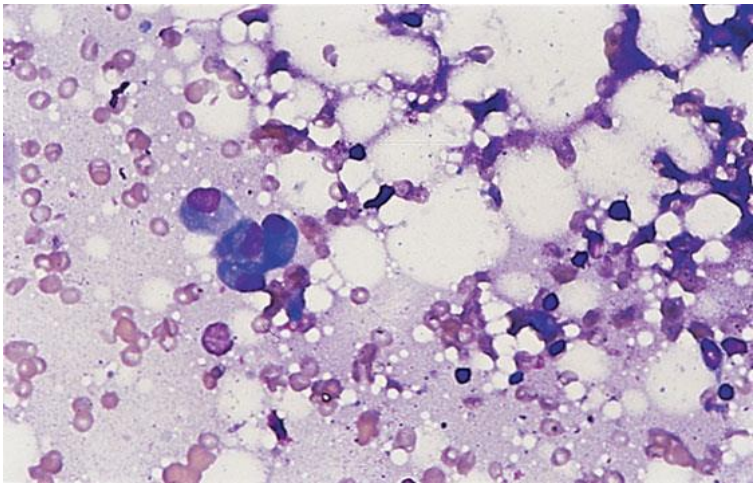


Figure 4: Hematopoietic cells in the bone marrow decreased and adiposity increased.

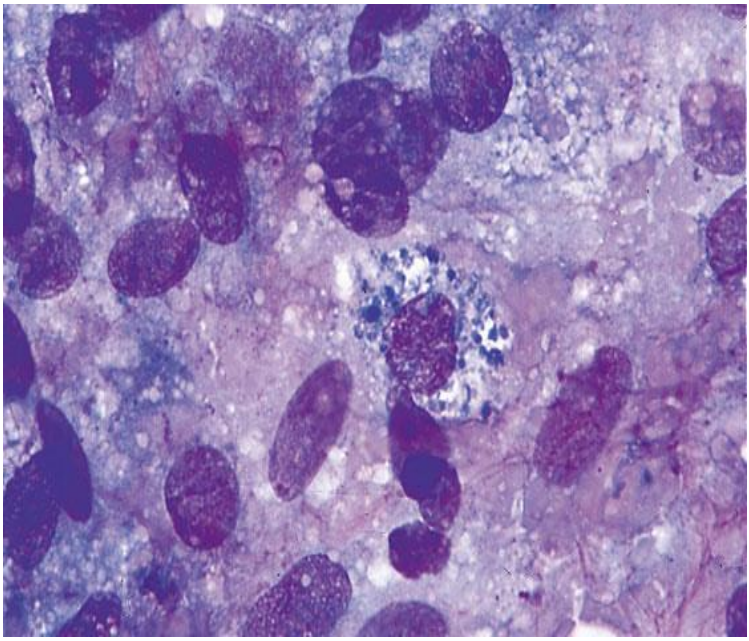


Figure 5: Aplasia in a patient who developed graft-versus-host disease due to transfusion.

Iron Deficiency Anemia

Hypochromia, poikilocytosis, microcytosis and anisocytosis are prominent in red blood cells. Reactive thrombocytosis may be seen. In severe anemia, pencil-shaped erythrocytes can be seen.

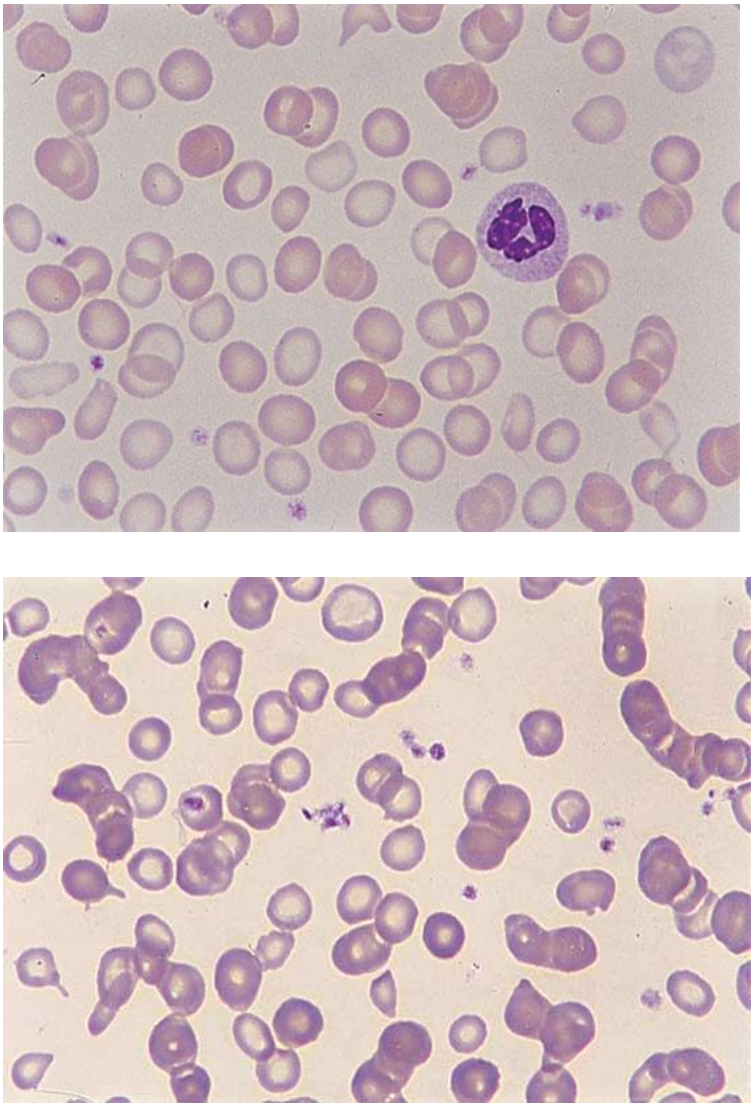
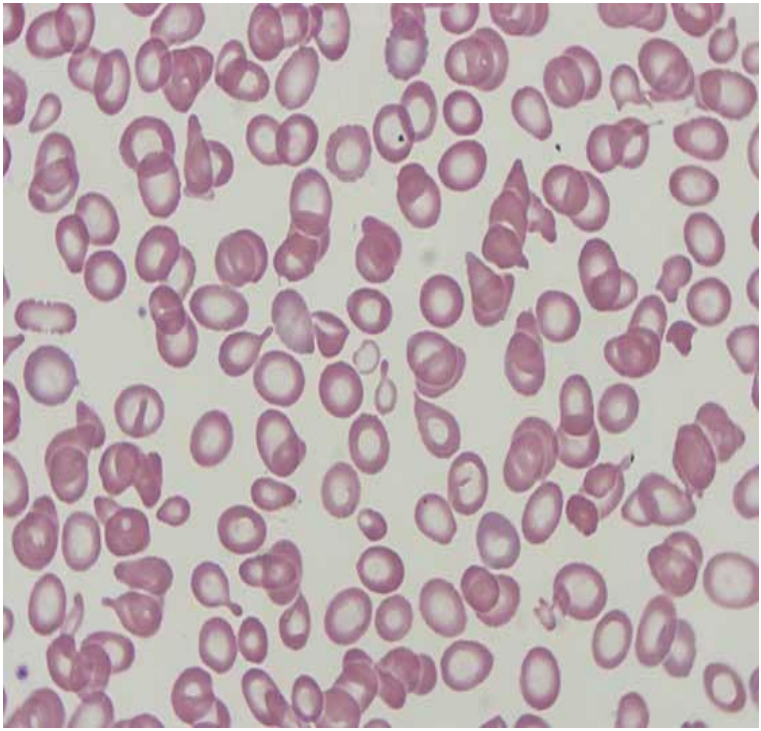


Figure 6: Hypochromic erythrocytes in peripheral smear.

HbH Disease

An important diagnosis in this disease is the presence of hemolysis and reticolysis. Peripheral smear shows hypochromia, microcytosis, target cells and Heinz bodies (beta chain precipitates). In this type of patients, icterus and splenomegaly are seen.



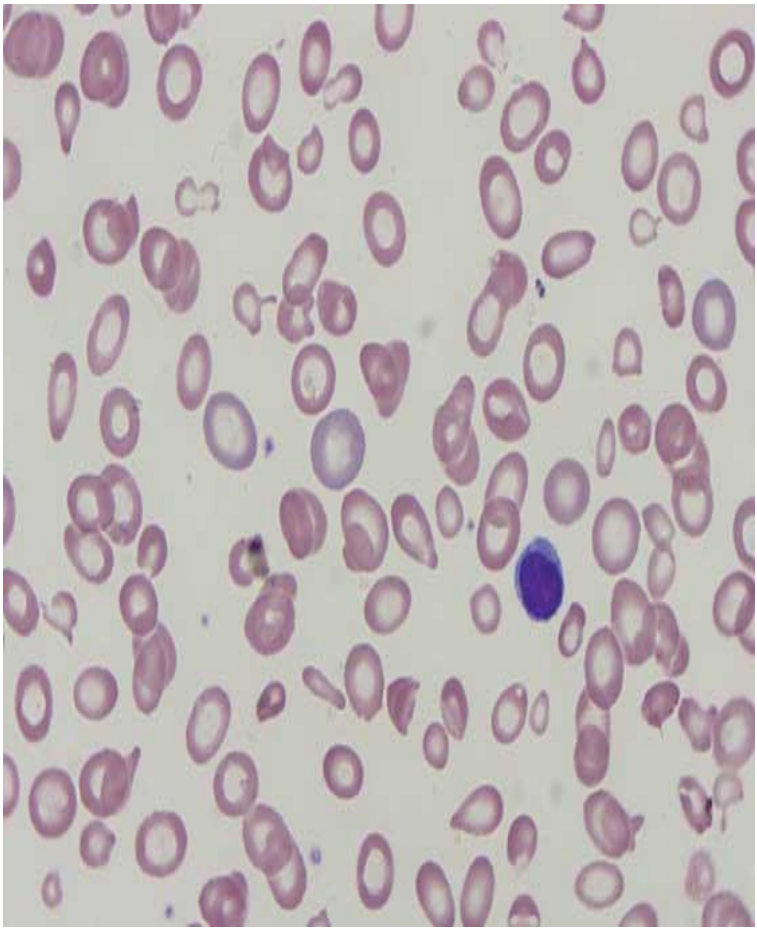


Figure 7: Anisocytosis, poikilocytosis and hypochromia of erythrocytes in peripheral blood.

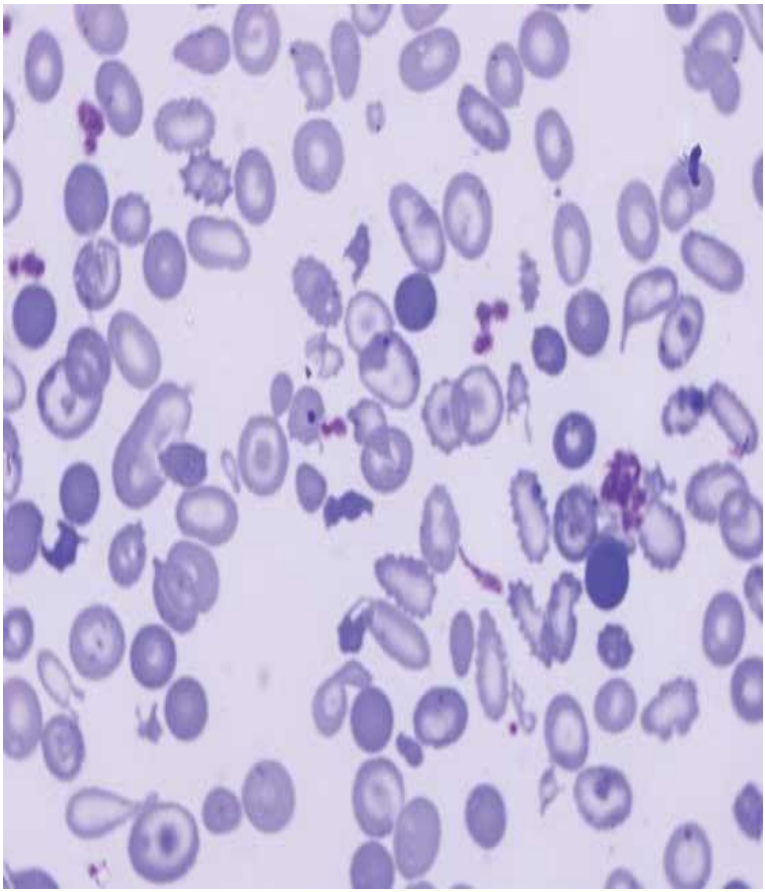


Figure 8: Reticulocytosis due to chronic hemolysis.

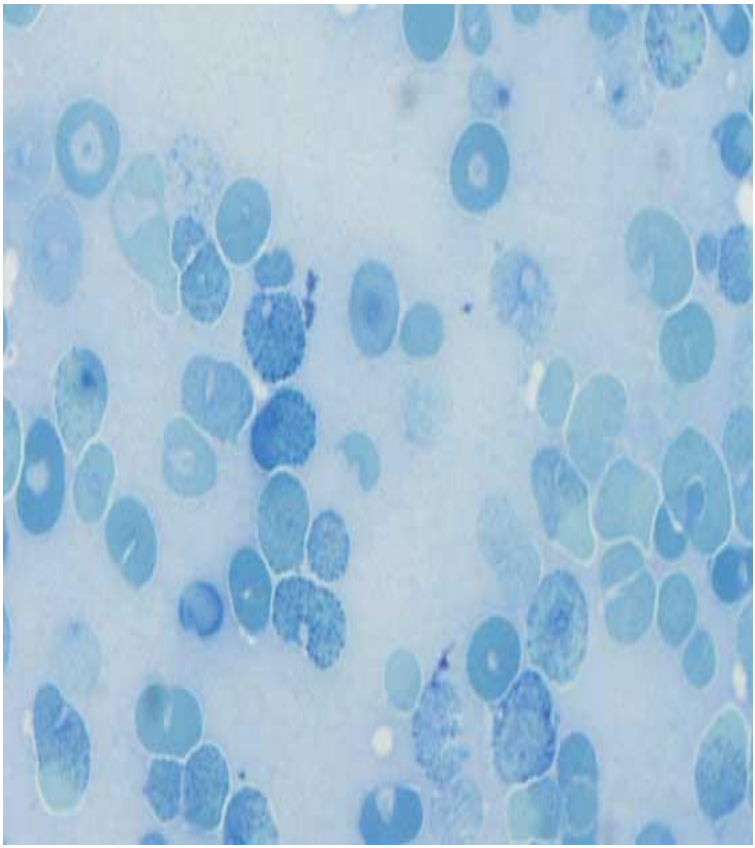


Figure 9: Golf ball appearance in erythrocytes in reticulocyte stain.

Megaloblastic Anemias

In this anemia, the main diagnosis is made by bisopenia or pancytopenia. In this disease, folate deficiency has a more severe course than B12 deficiency. Reticulocytopenia is present because there is no bone marrow response to anemia. Reticulocyte response is more severe in megaloblastic anemia than in iron deficiency anemia. Peripheral smear shows neutrophil hypersegmentation, macroovalocytosis and normoblasts. Howell-Jolly bodies are seen in red blood cells. In bone marrow aspiration, megaloblastic changes, metamyelocyte, hypersegmented formation in megakaryocytes and erythroid hyperplasia are present. In the cellular bone marrow, the number of proerythroblasts and basophilic erythroblasts and the basophilia of their cytoplasms are increased. Due to hemolysis, serum iron increases and haptoglobin decreases.

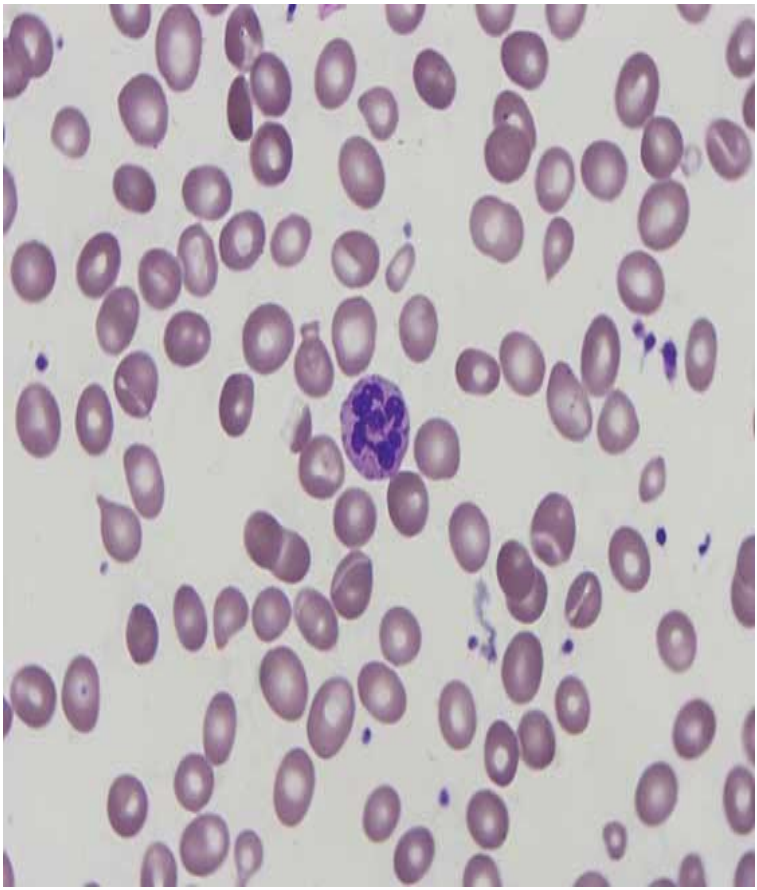


Figure 10: Anisocytosis, macroovalocytosis, hypersegmentation of neutrophils in peripheral smear.

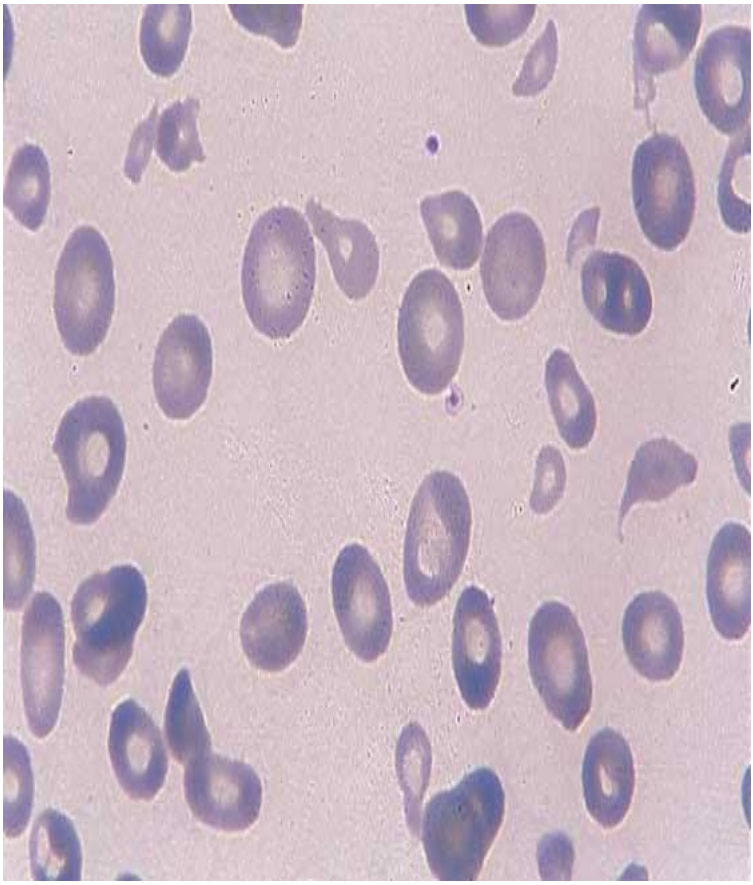


Figure 11: Macroovalocyte-type erythrocytes in megaloblastic anemia in peripheral smear.

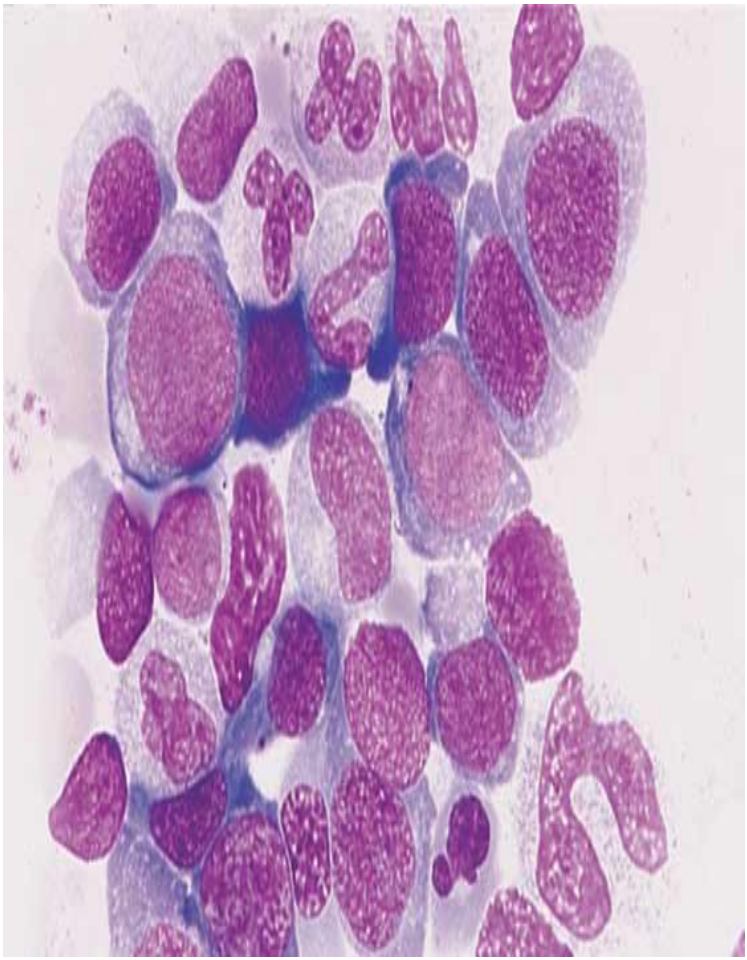


Figure 12: Metamyelocytes in bone marrow megaloblastic anemia.

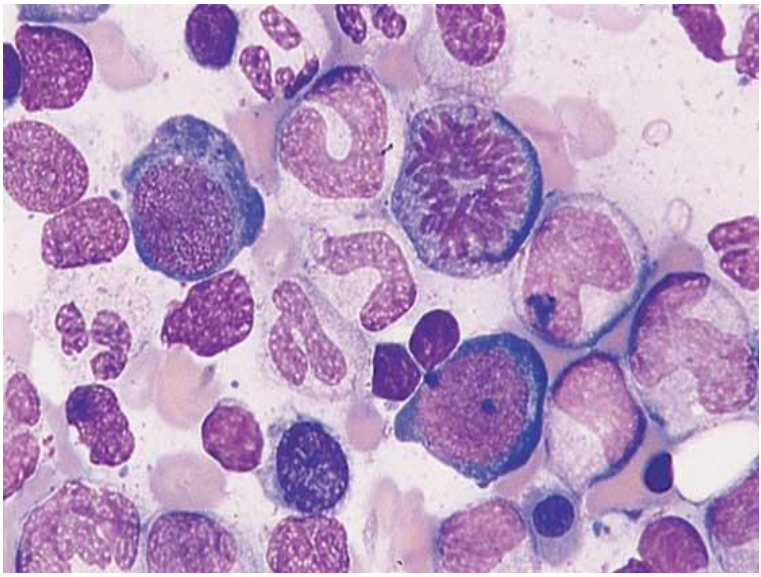


Figure 13: Large pronormoblasts with clear blue cytoplasm in the bone marrow, cells in mitosis and giant stabs and metamyelocytes.

Sickle Cell Anemia

In the peripheral smear, normochromic normocytic anemia, sickle-shaped erythrocytes, basophilic spotting in erythrocytes due to impaired spleen functions and Howell-Jolly bodies can be seen. Anemia in patients is due to shortened erythrocyte lifespan. Leukocytosis, mostly

consisting of normoblasts, draws attention in patients with autosplenectomy.

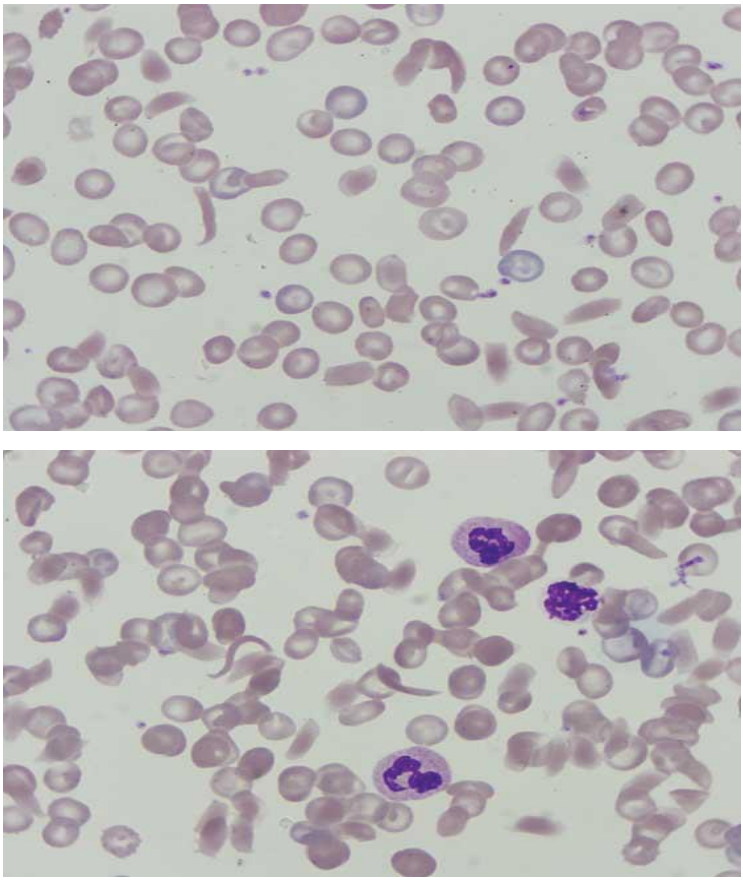


Figure 14: Polychromasic, target cell and sickle-shaped erythrocytes in peripheral smear.

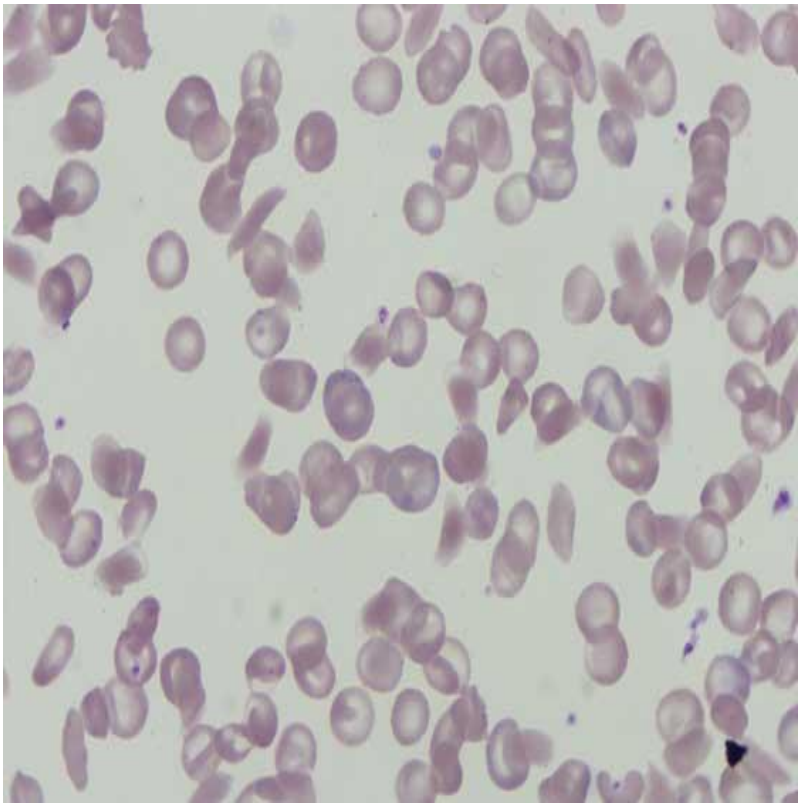


Figure 15: Polychromasic and sickle-shaped erythrocytes in peripheral smear.

Polycythemia Vera

Patients have high hemoglobin, hematocrit (Hct), and erythrocyte counts. Hb varies between 18–24 g/dL. The

upper normal limits of hematocrit are >48% in women and >51% in men. If the hematocrit is >56% in women and >60% in men, it is absolute erythrocytosis. There is moderate leukocytosis, basophilia, eosinophilia, and thrombocytosis, mostly of mature neutrophils. The platelet count is usually above 500000/microl. In peripheral smear, prominent anisocytosis, poikilocytosis, nucleated and teardrop-shaped erythrocytes in erythrocyte morphology suggest myelofibrosis except polycythemia vera. It is frequently seen in the advanced stages of the disease because it transforms into myelofibrosis. Giant platelets or megakaryocyte particles are often present, especially during conversion to myelofibrosis. Since hydroxyurea is frequently used in patients, drug-induced macrocytosis in erythrocytes and hypersegmentation in neutrophils are observed. When the patients first come, their facial appearance is dark red in color, that is, pleatory, due to the increased erythrocyte mass.

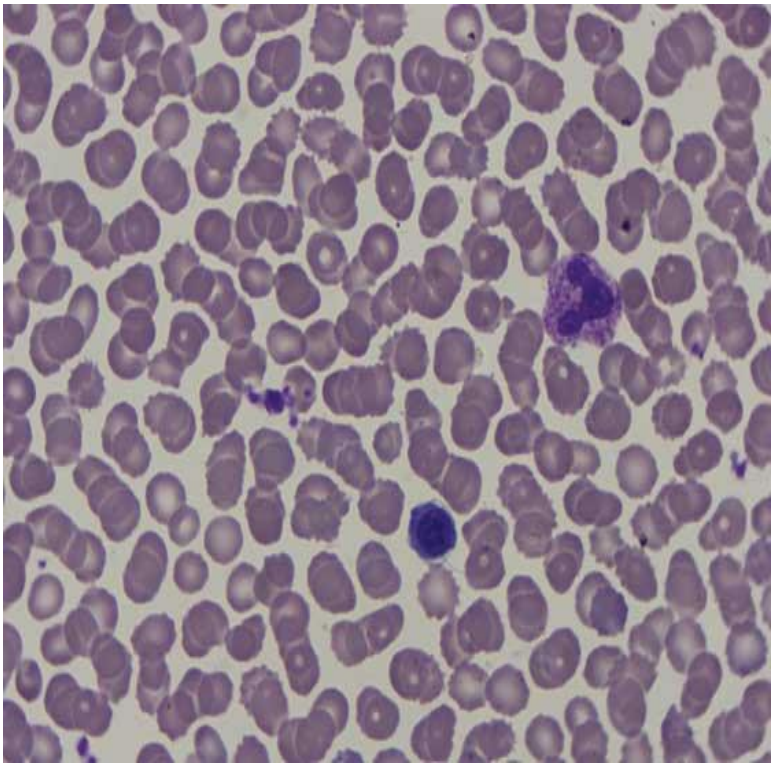


Figure 16: Nucleated erythrocytes, neutrophils, large platelets in peripheral smear.

Malaria

Parasites in the form of "signet ring" in erythrocytes are typical. It can be seen in different forms in erythrocytes depending on the life cycle of the parasite. While the

Falçiparum form is not seen in our country, it is now seen due to international business and touristic trips in recent years. Its appearance in the form of a "banana" is typical.

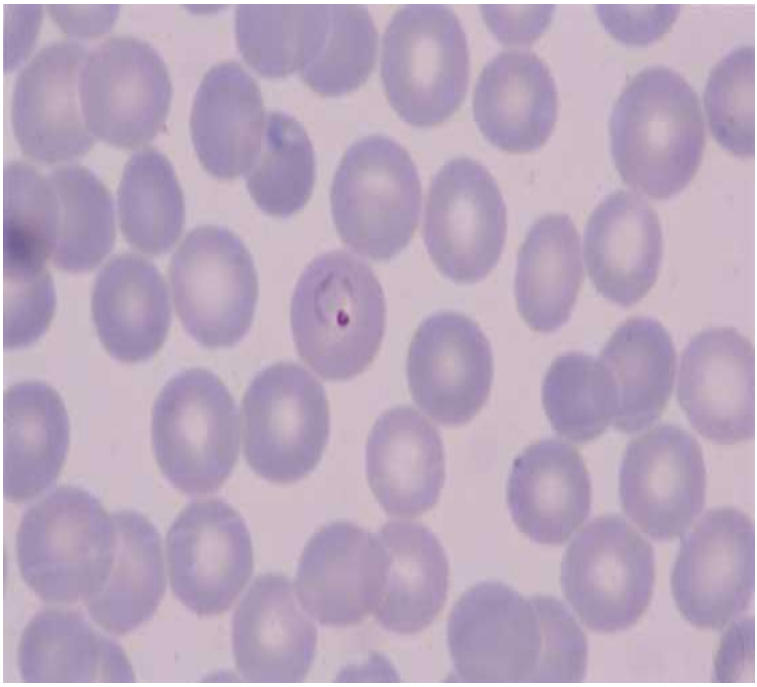


Figure 17: Signet ring appearance in erythrocyte in peripheral smear.

If we look at megaloblastic anemia, it has been revealed that it is caused by damaged DNA synthesis, which are its hematopoietic precursors. It has been suggested that this

results in so-called ineffective red blood cell production (erythropoiesis) and intramedullary hemolysis. Macrocytic anemia, defined as greater than 100 fL, is known to be the hallmark of megaloblastic anemia. However, leukopenia and thrombocytopenia are also common. One of the biggest causes of this condition, which we call megaloblastic anemia, is due to vitamin B9 or vitamin B12 deficiency. In addition to these, we can name the less common causes as congenital disorders, drugs, micronutrient deficiencies and exposure to nitrous oxide [18]. Since Vitamin B 12 is produced only by microorganisms, studies have shown that it is almost found in foods of animal origin. Vitamin B 12 is normally found in body stores as 3 to 5 mg. However, the recommended adult daily intake has been found to be 2.4 μg [19].

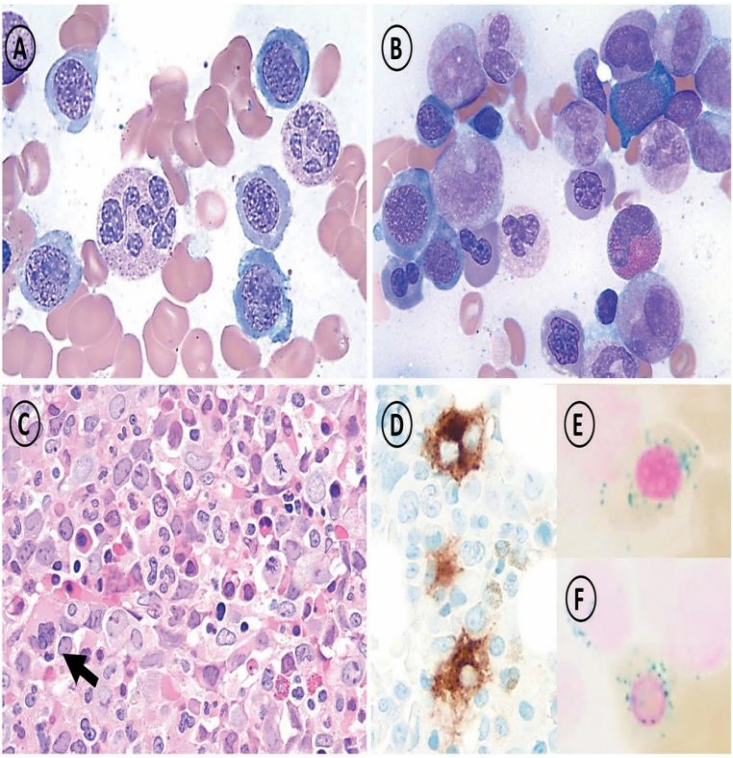


Figure 18: A, B: When we look at bone marrow aspirate smears that show very intense megaloblastic changes, nuclear cytoplasmic synchronization, binucleation, nuclear disorder in erythrocyte cells as well as hypersegmentation and Wright band forms in giant metamyelocytes (Giemsa, × 1000). C : Bone marrow core biopsy (hematoxylin and eosin, x 400) indicated by

hypercellularity, erythroid hyperplasia, left shift in maturation as well as megakaryocytes (arrow) with small dysplastic structure. D : In the core biopsy, there are small dysplastic megakaryocytes stained with CD61 and immunohistochemistry shown. In addition, E, F: when we examine, an increase in the iron point called aspiration smears, annular lateral eruptions are distinguished. In the case of macrocytic anemia (>1% of neutrophils with 6 or more nuclear lobes or >5% of neutrophils with 5 nuclear lobes), hypersegmented neutrophils are considered specific for megaloblastic anemia and are rarely seen in other diseases [19]. Severe anemia is very rare in patients with COVID-19 pneumonia. It has also been suggested that the hemoglobin (Hb) concentration tends to decrease gradually during the course of the disease. It has enormous effects on the effect of red cells on morphology and survival in patients in both sepsis and hypoxia states. This situation reveals the studies that have contributed to the pathogenesis of COVID-19 anemia as it has a complex structure. Especially if we consider the period when this epidemic peaked in Northern Italy, it has been suggested in studies that 39% of hospitalized patients needed

transfusion support 15 days after hospitalization. It has been revealed that in almost half of most patients with severe COVID-19, antibodies bound to red blood cell (RBC) are detected by direct antiglobulin test (DAT). In particular, studies have shown that their presence is associated with lower Hb levels and higher transfusion requirements [20]. A previously healthy 46-year-old woman came to the hospital with some complaints, and flu-like symptoms were observed before she was hospitalized. Later, chest X-ray and chest computed tomography were taken, and pneumonia symptoms were detected. Subsequently, as a result of radiology studies, it was determined that lung findings worsened and respiratory symptoms requiring intubation and ventilation were intense. In such a case, the transfer of the patient to the university hospital, which is much more detailed and developing, was ensured.

According to the data obtained as a result of the transfer to the university hospital, it was concluded that it was positive for (COVID-19). Initial complete blood count (CBC), lymphopenia (200/μL), normocytic anemia

(hemoglobin = 10.4 g/dL) and a normal platelet count (213 × 103/μL) with a normal leukocyte count (7.3 x 103/μL)) showed. Three days after transfer to the university hospital, the patient developed leukocytosis (14.1 × 103/μL), which led to evaluation of the peripheral blood smear with a left-shifted neutrophilic cell population. Persistent lymphopenia and mild monocytosis (900/μL) were also detected. The peripheral blood smear was found to be consistent with a leukoerythroblastic picture with normocytic anemia, with occasional nucleated red blood cells (Figure 1A), mild anisocytosis, and rare dachrocytes. Schistocytes were absent. Left-shifted myeloid cell neutrophils, including occasional myelocytes and rare promyelocytes, were noted (Fig. 1B-D). Lymphopenia was confirmed with many of the stained cells seen. Although the platelets were at a sufficient level, large platelets were also observed.

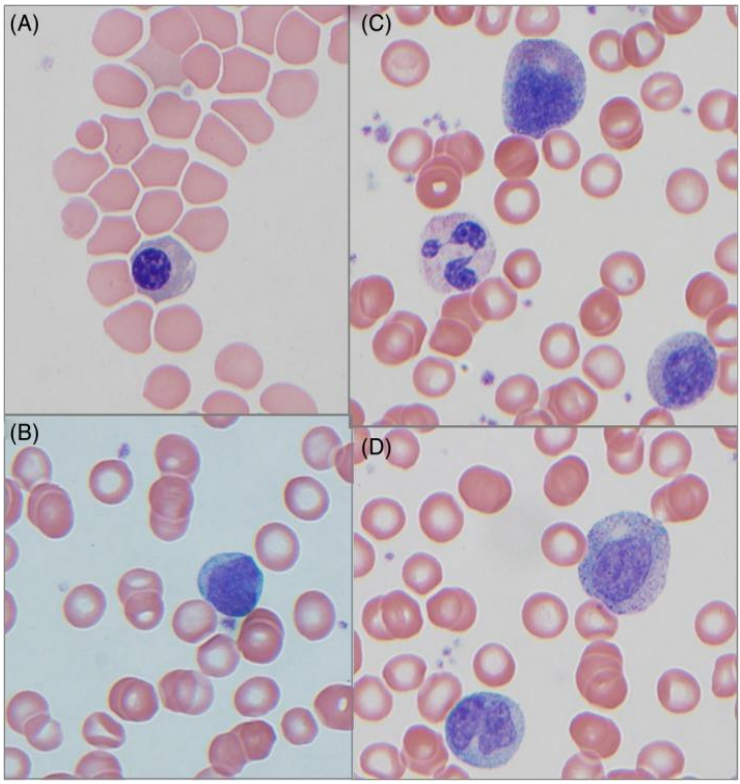


Figure 19: Review of peripheral smear at X100 magnification, nucleated erythroid with prominent nucleoli and immature chromatin pattern, A, rare blast, B, left-shifted myeloid series with immature promyelocytes and metamyelocytes, C, and occasional monocytes,

Leukoerythroblastic reactions, defined as immature erythroid and immature myeloid cells circulating in the peripheral blood, are rare. Leukoerythroblastic blood manifestations are typically seen in bone marrow fibrosis-related disorders, including myelofibrosis and other myeloproliferative disorders, and in cancers with metastatic disease to the bone marrow. Leukoerythroblastosis can rarely be seen in viral infections such as parvovirus. [21].

Leukocytes (White Blood Cells): They are cells that are grayish white in color and have a nucleus. Their size is between 7-20 microns. There are 65000-10000 leukocytes in 1mm3 blood in humans, 9000 in dogs, 10000 in cats, 9000 in horses, 8000 in cattle, 12000 in sheep and goats, 15000 in pigs, 28000 in chickens. An increase in the amount in the blood is called leukocytosis, and a decrease is called leukopenia. Leukocytes are defense system cells. They are classified according to the presence of granules in their structure. Those that contain granules are called granulocytes, those that do not are called agranulocytes. The amount of leukocytes is high in early ages. The

amount of leukocytes increases during digestion and after active movements. Pathologically, an increase in leukocytes is called leukocytosis, and a decrease is called leukopenia. Studies show that adult T-cell leukemia/lymphoma (ATLL) is a mature T-cell lymphoproliferative disorder associated with human T lymphotropic virus (HTLV-1) infection. It consists of pleomorphic cells with irregular nuclear borders, often called flower cells. Generally, this condition shows a significantly aggressive clinic and many studies show that it is directly related to poor outcomes [22]. It significantly affects individuals in HTLV-1 endemic areas, such as Japan, parts of Africa, South America and the Caribbean, where ATLL is most common. It has recently been suggested that the incidence of the disease has increased drastically due to heavy travel and immigration in Europe and the United States, particularly south Florida [23]. In a study, Shah et al. It documented a marked increase in ATLL cases in the US, where New York appears to be the state with the majority of reported cases [24]. Although the average age of the patients varies from region to region, the age of onset of the disease usually occurs 20-30 years

after the infection, and the average age range is set to be 43-65 years. Rare cases in children, especially in Brazil, do not preclude the diagnosis at this age. The number of aka women is more. Notably, Survival is associated with the clinical presentation variant, but median survival is lowest in patients with aggressive disease and highest in patients with chronic or smoldering ATLL (table 1). However, according to SEER data, the 5-year overall survival of all patients with ATLL is low, at 23.4%.

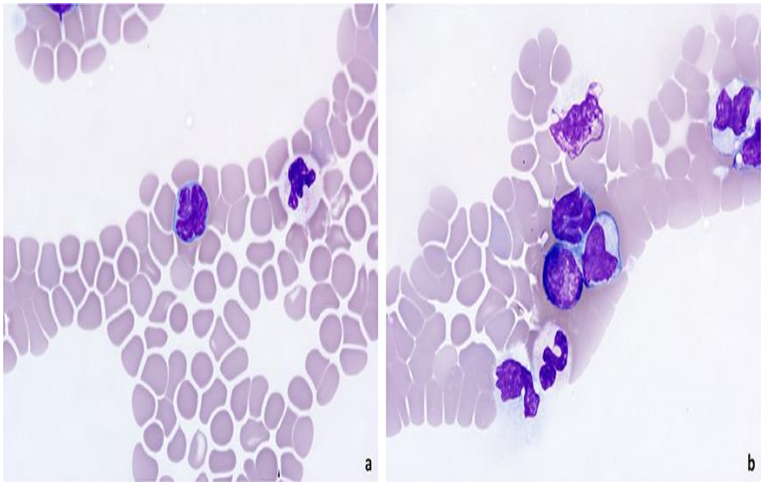


Figure 20: (a, b) Characteristic 'flower cells' (Diff-Quick blot 1000x) seen in ATLL.

Lymph nodes affected as a result of the disease show moderate pleomorphism. It has been demonstrated in studies that it shows paracortical enlargement with T cell infiltrates with abnormal structure, especially consisting of small to medium cells [25]. When we look at the lymph node distribution, Hodgkin-like, anaplastic large cell lymphoma, pleomorphic small cell type, pleomorphic type and angioimmunoblastic T cell lymphoma type have been revealed. Anaplastic large cell lymphoma exhibits a sinusoidal structure. In particular, it has been suggested that there is typically at least moderate CD30 expression. When we look at the precursor lymph node lesions, it can be detected in people infected with HTLV-1, and studies have shown that it has a classically called Hodgkin-like or lymphadenitis-like morphology [26].

It has been suggested that the use of ATLL differential diagnosis can be distinctive in order to avoid misdiagnosis when any of the described morphologies are encountered in endemic regions that do not show the effect of HTLV-1 due to these morphologies resulting from these studies and explanations [27].

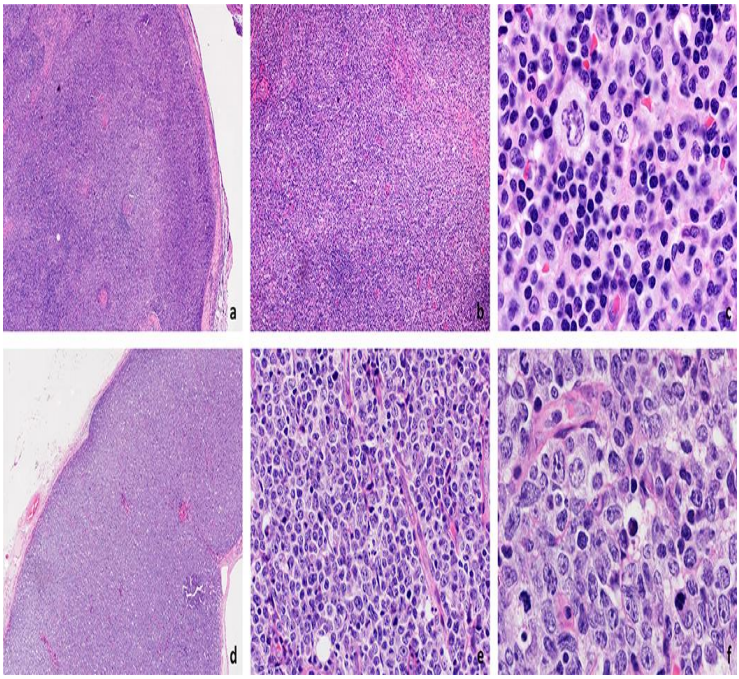


Figure 21: Lymph node features in ATLL. (a) Architecture is deleted with normal follicle loss (40x). (b) infiltrated lymphoma cells have variable size (100x). (c) Closer examination of malignant cells shows polylobate lymphocytes and Hodgkin-like cells (600x). (d) Diffuse infiltration by lymphoma cells (40x). (e, f) This is an example of ATLL with pleomorphic morphology (400x and 600x).

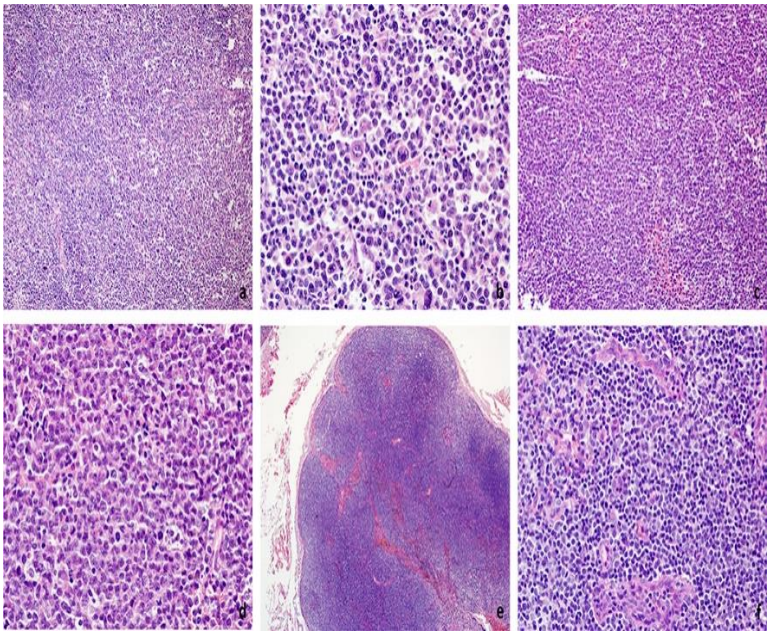


Figure 22: Histological subtypes of ATLL. (a, b) anaplastic large cell lymphoma-like (200x and 600x). (c, d) Burkitt-like pattern (200x and 600x). (e, f) Small cell, pleomorphic type (20x and 600x).

Bone marrow involvement, irregular interstitial distribution, or extensive involvement [26] Osteoclast activation is often noted and contributes to hypercalcemia and lytic lesions. Bone marrow involvement is usually seen in acute ATLL and may be encountered in chronic

and lymphomatous forms, therefore routine bone marrow evaluation should be considered if present.

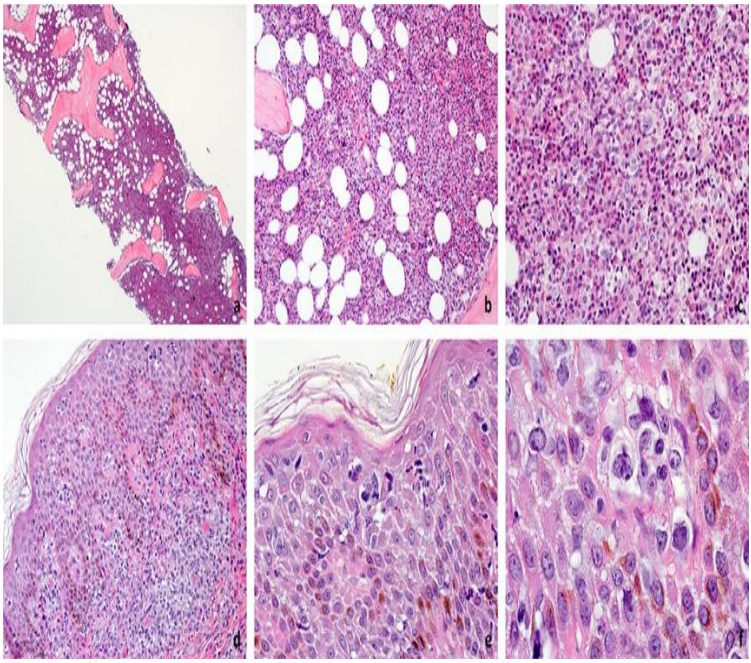


Figure 23: Bone marrow involvement in ATLL. (a) an interstitial spread pattern is present on the core biopsy (40x). (b and c) Closer examination shows highly pleomorphic and abnormal lobed lymphoma cells (200x and 600x). Skin involvement in ATLL. (d) A band-like and epidermotropic leak is present (200x). (e and f) Skin invasion is similar to mycosis fungoides with

epidermotropism and the presence of Pautrier microabscesses (600x and 1000x).

ATLL is usually derived from CD4+ helper T cells and therefore shares similar immunophenotype to regulatory T cells. 1 Neoplastic cells are usually positive for pan T-cell antigens such as CD2, CD3, CD5 with partial loss of CD7 (the latter occurring in almost all cases) [28].

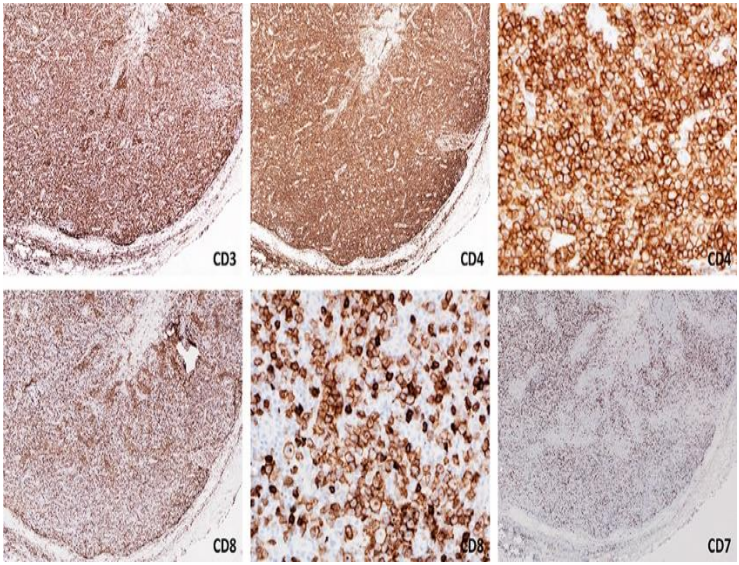


Figure 24: Immunohistochemistry in ATLL. Tumor cells are positive for CD3 and CD4. A subset of malignant cells

show co-expression of both CD4 and CD8. Abnormal CD7 loss is seen in the vast majority of tumor cells.

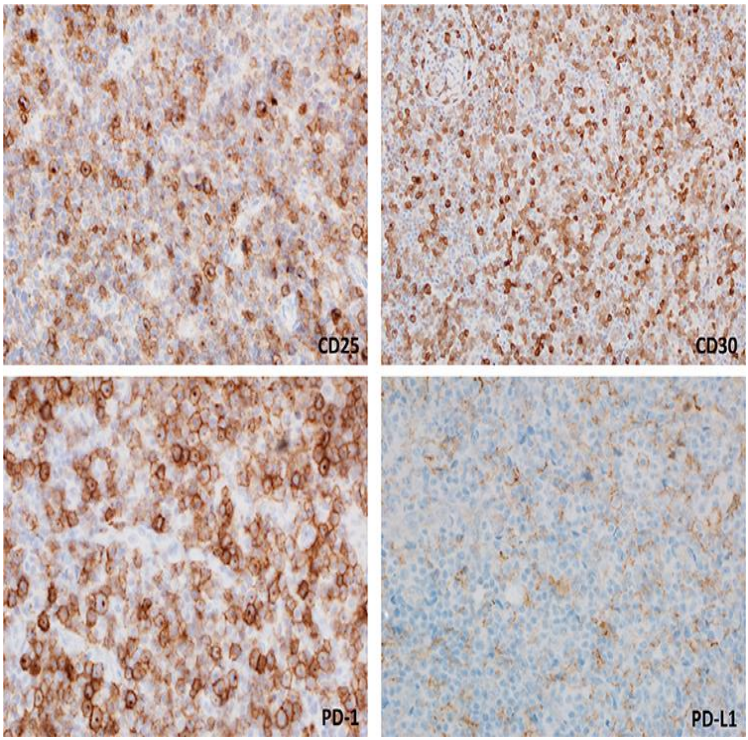


Figure 25: Immunohistochemistry in ATLL. Tumor cells are commonly positive for CD25. The majority of neoplastic cells are positive for CD30. In this case, PD-1 is positive in most cells, while PD-L1 is positive in a smaller proportion of cells.

The development of ATLL is associated with an estimated 5 or more genetic hits that contribute to leukemia/lymphomagenesis as well as HTLV-1 infection. From a practical point of view, clonal T cell receptor rearrangement is identified in most/all ATLL cases [29]. Although viral integration studies are required to diagnose ATLL in endemic regions (eg, Japan), such genomic studies are not clinically available in the USA. Therefore, in most cases, the presence of a T-cell lymphoma and a positive serology for HTLV-1 in an individual from an endemic region is considered important for the diagnosis of ATLL [30].

Acute Lymphoblastic Leukemia

The leukocyte count is variable at the time of diagnosis in ALL patients. Leukocytosis is seen in 2/3 of the cases (60-70%) due to blasts in the peripheral blood. Hyperleukocytosis is observed in 10-20% of cases (>100,000). At the rate of 30%, the leukocyte count is <5,000/mm3. In this case, blasts are rarely seen in peripheral blood and diagnosis becomes difficult.

Cytochemical stains are necessary in diagnosis and differential diagnosis In histochemical analyzes, in 70% of the cases, PAS stain is (+) in the cytoplasm as blocks MPO, SBB, naphthal ASD chloroacetate esterase and non-specific esterase (-) Terminal-deoxynucleotide transferase (TdT) in the nucleus (+) and can be detected in more than 80% of cells.

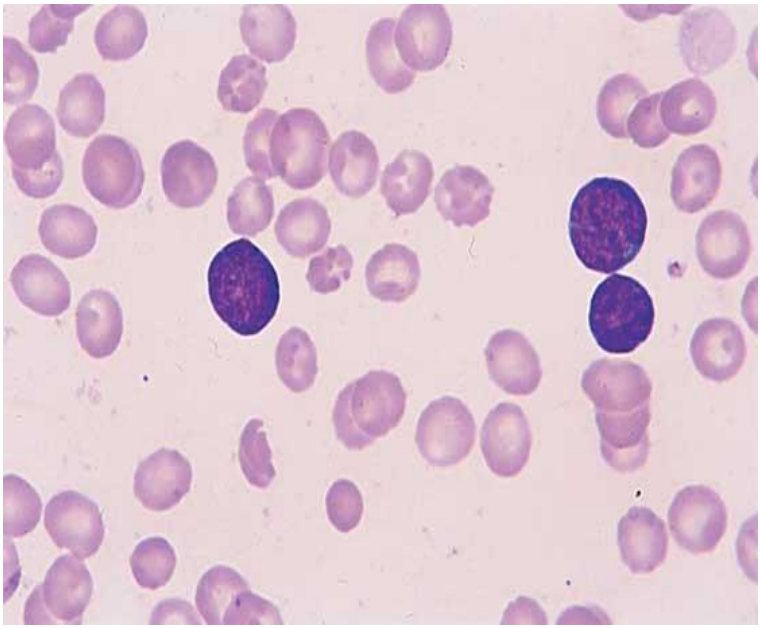


Figure 26: Lymphoblasts with indistinguishable cytoplasm and nuclei are seen in peripheral smear.

Acute Myeloblastic Leukemias

Diagnosis is based on the appearance of typical blasts in the peripheral blood. However, not every patient may have leukemic cells in the peripheral blood. This condition is called aleukemic leukemia. In this case, the diagnosis is made with an increase in blasts in the bone marrow examination.

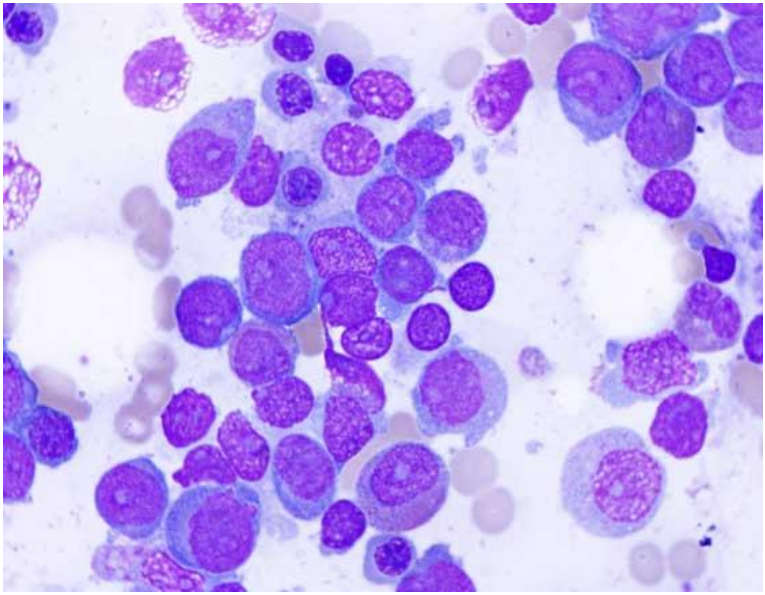


Figure 27: Myeloblasts with clear nuclei and fine chromatin network are seen in the patient's bone marrow.

Hairy Cell Leukemia

Pancytopenia can be defined by the detection of splenomegaly, large, mononuclear cells with hair-like cytoplasmic projections in the blood, bone marrow, and spleen. 20% of patients have leukocytosis. Since the patients have fibrosis in the bone marrow, bone marrow is not taken in aspiration. For this reason, a bone marrow biopsy should be performed. In HCL, neoplastic B cells are larger than chronic lymphocytic leukemia cells. The cytoplasm of the cells is more abundant and has fringe-like extensions. Cells show strong tartrate-resistance isoenzyme-5 acid phosphatase (TRAP) activity. TRAP positivity is useful for diagnosis. In contrast to B-CLL, cells in HCL express high levels of CD11c, CD25 and CD103. CD19, CD20, surface Ig and plasma cell antigen-1 (PCA-1) are positive due to B lymphocyte disease.

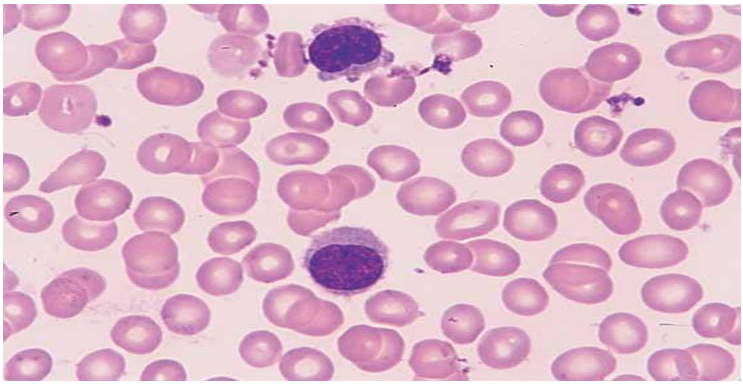


Figure 28: In the peripheral smear, hairy cell cells with hair-like projections in their cytoplasm are seen in the middle.

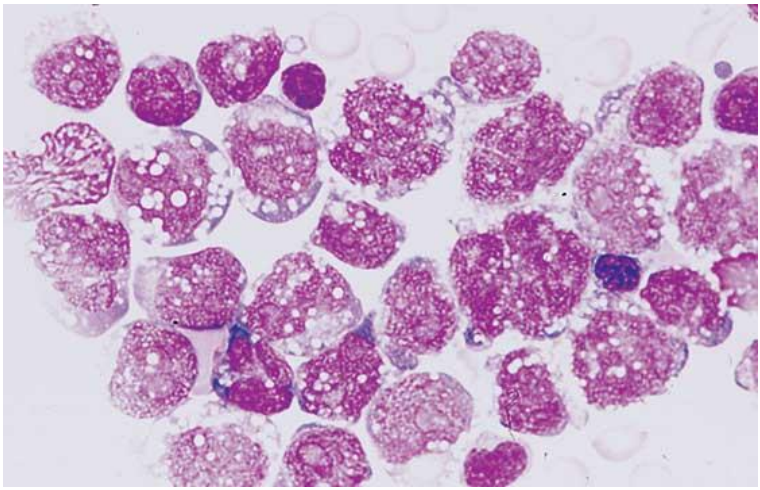


Figure 29: Burkitt Lymphoma

Lymphoma cells with cytoplasm and vacuole are seen in the abdominal fluid.

Plasma Cell Diseases

Plasma cells are cells with a blue cytoplasm, located off-centre, with a size of 8-20 microns. Cells with nucleolus in the nucleus are called anaplastic plasma cells. Cells whose cytoplasm is stained red are flame cells. Those that contain grape-shaped immunoglobulin in their cytoplasm are mott cells. The roll formation seen in erythrocytes in peripheral smears of myeloma patients is typically due to an increase in monoclonal protein.

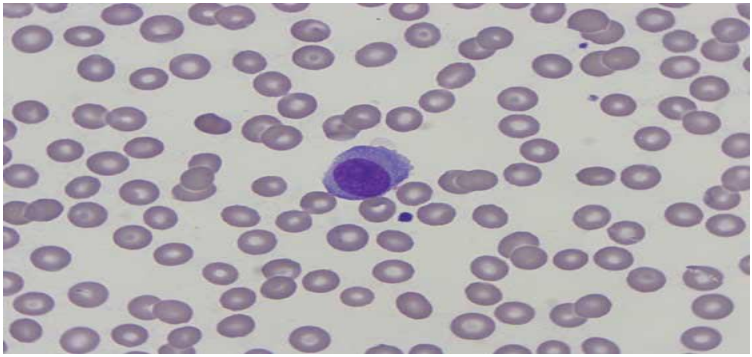


Figure 30: In the peripheral smear, a plasma cell with basophilic cytoplasm and a mid-outer nucleus is seen.

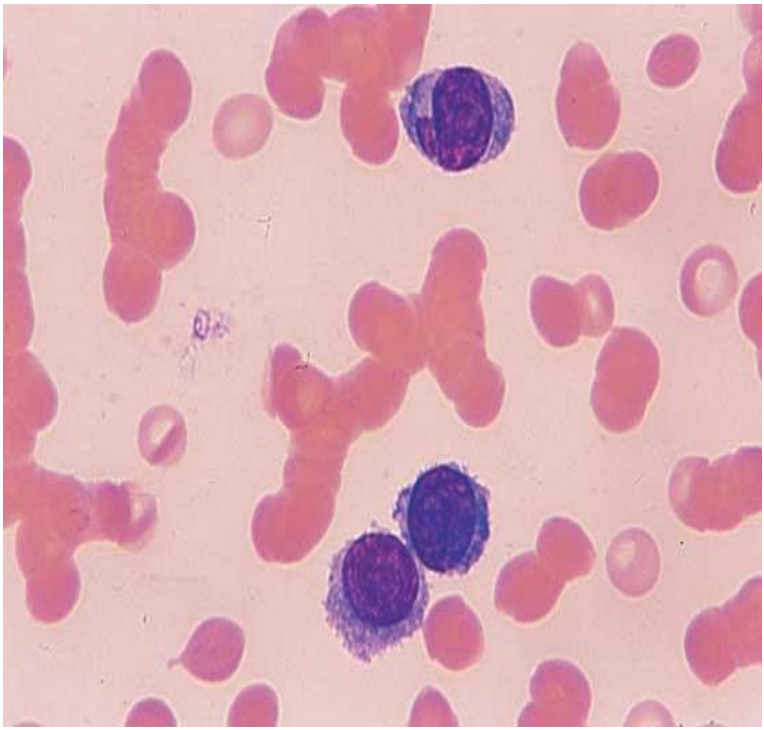


Figure 31: Plasma Cell Leukemia

Roll formation and plasma cells are seen in the peripheral smear.

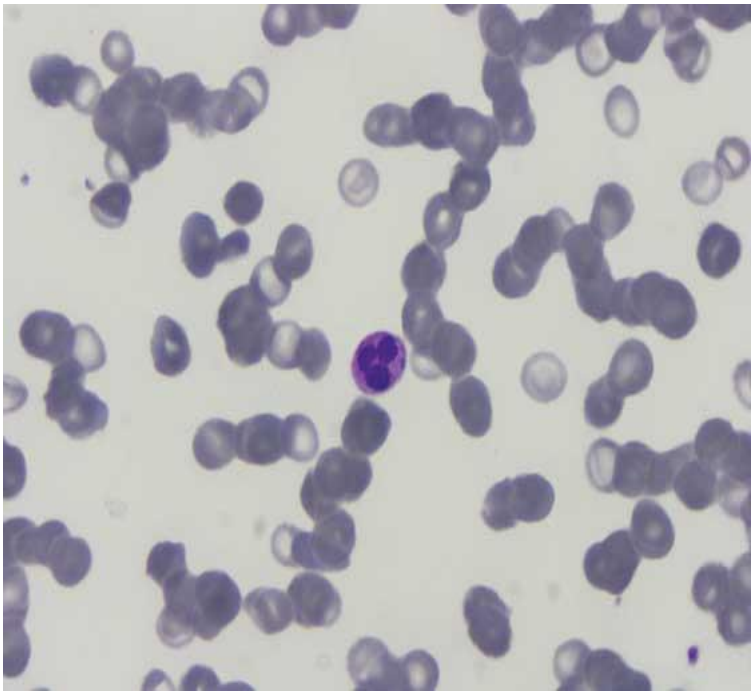


Figure 32: Döhle Body

In the peripheral blood smear of a patient with acute lymphoblastic leukemia, after chemotherapy, the neutrophil is seen as a blue bar in the cytoplasm.

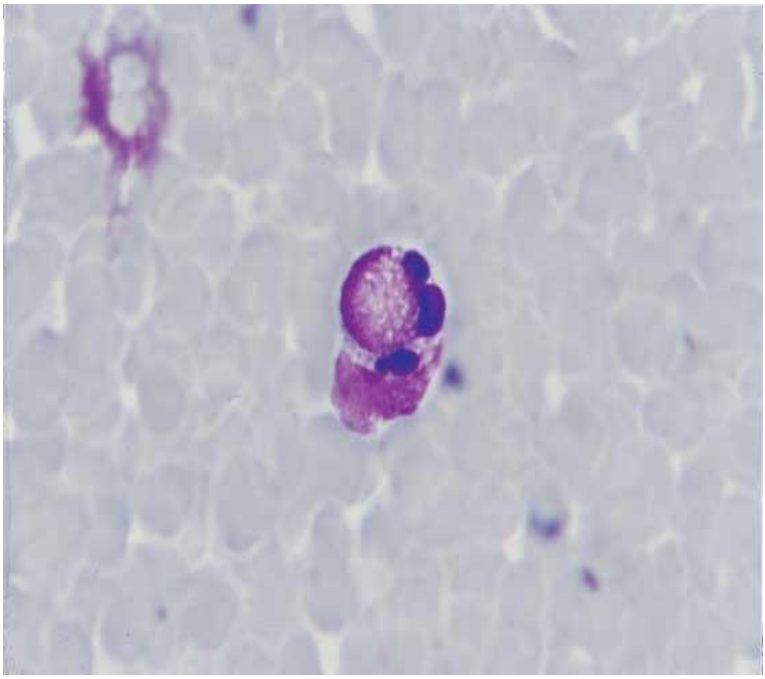


Figure 33: Lupus Cell

They are cells in which the neutrophil cytoplasm is homogeneously pinkish stained and the neutrophil nuclei are pushed aside. It is prepared from buffy coat. It is seen in patients with systemic lupus erythematasus.

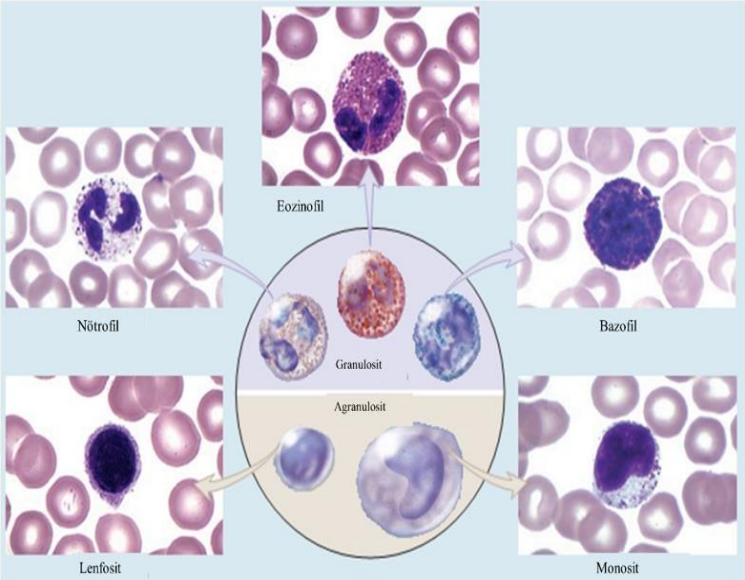


Figure 34. https://cdn-acikogretim.istanbul.edu.tr/ Temel _anatomi_ve_histoloji_bilgisi/13/index.html

a) Agranulocytes: The nuclei of these cells consist of a single piece. They are called mononuclear leukocytes. They do not contain granules in their cytoplasm. Agranulocytes are not fully differentiated. For this reason, they can complete their differentiation when they go out of the blood vessels (connective tissues and blood-forming organs).

Lymphocyte

Cell size varies between 7-18 microns. The nucleus/cytoplasm ratio is in favor of the nucleus and is approximately 3-5/1. The nuclear chromatin network is dense. The nucleus is round and usually located in the middle of the cell. Cytoplasm is in light or dark shades of blue. Sometimes large granules may be present in lymphocytes with large diameters and large cytoplasms. They are found in 20–40% of peripheral blood smears.

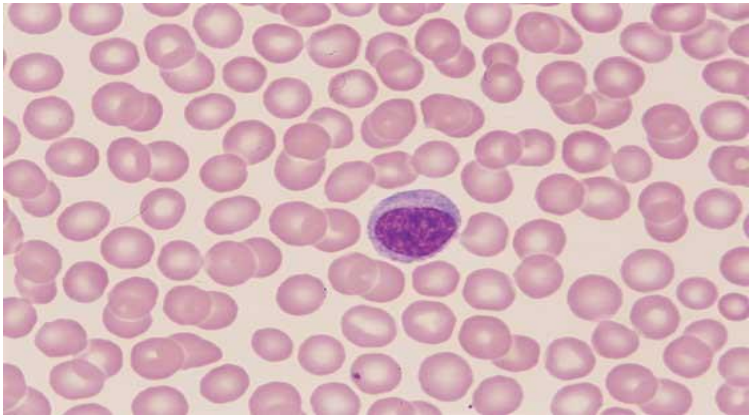


Figure 35: In the peripheral blood smear, the cytoplasm is blue and the nuclear chromatin network is coarse lymphocyte.

MONOCYTE

It is one of the large cells seen in peripheral blood smear. It usually varies between 12-20 microns in diameter. The nuclear chromatin network is loose and convoluted in shape, resembling a kidney or bean. Seen from the top, the core looks like a cauliflower. The nucleus is located in the middle or edge of the cell. The cytoplasm is gray-blue in color. Their cytoplasm contains fine granules. In infections, the granules are dark in color and may contain in vacuoles. Since there are cells that migrate into the tissue and turn into macrophages, there may be protrusions in the form of pseudopods on the cell wall. It is found in 6–10% of peripheral blood smear.

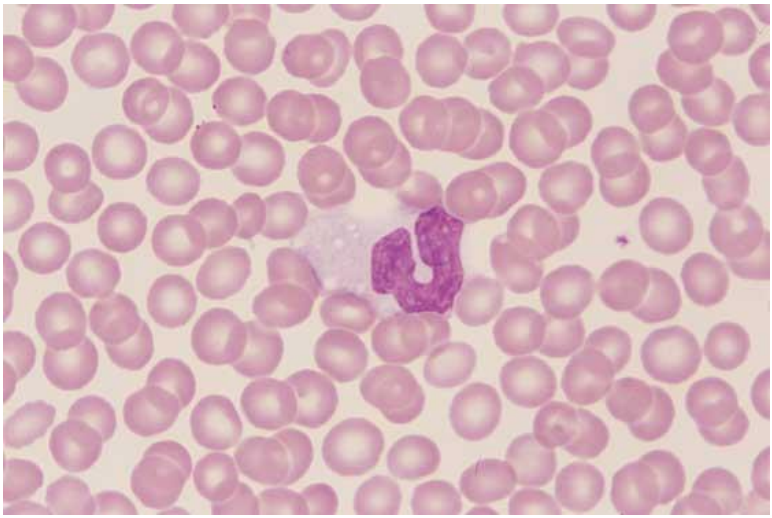


Figure 36: Peripheral smear shows a monocyte with a gray cytoplasm and a coiled nucleus.

Granulocytes: There are many granules in their cytoplasm. In granulocytes, the nucleus consists of several parts connected by thin bridges. Polymorphous nuclear leukocytes, Polynuclear leukocytes

- Nucleus is heterochromatic
- Since the granulocytes are motile, they can go out of the blood vessel, but they cannot enter the circulation again (agranulocytes can enter).

•Granulocytes do not have the ability to divide because they have excessive differentiation properties.

• Cells that are terminated or senescent in the connective tissues die and the remnants macrophages are destroyed.

Neutrophil granulocytes

They constitute 30-70% of all leukocytes. The most abundant leukocyte in the blood is the neutrophil granulocyte. Their size is between 10-12 microns. Their shape is round in circulating blood, they can be flattened when extravasated. Their abundant cytoplasm is poor in organelles. There are abundant granules in their cytoplasm. There are two groups of granules in the cells:

- Azurophil granules (primary granules)

-Special (specific) granules (secondary granules)

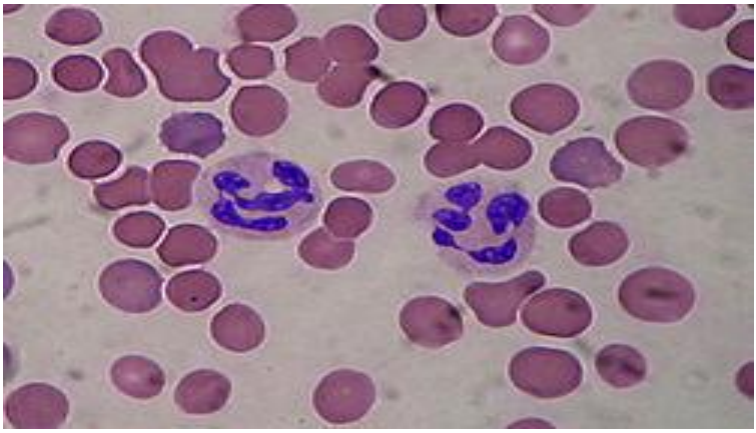


Figure 37: https://en.wikipedia.org/wiki/Neutrophil_polymorphs

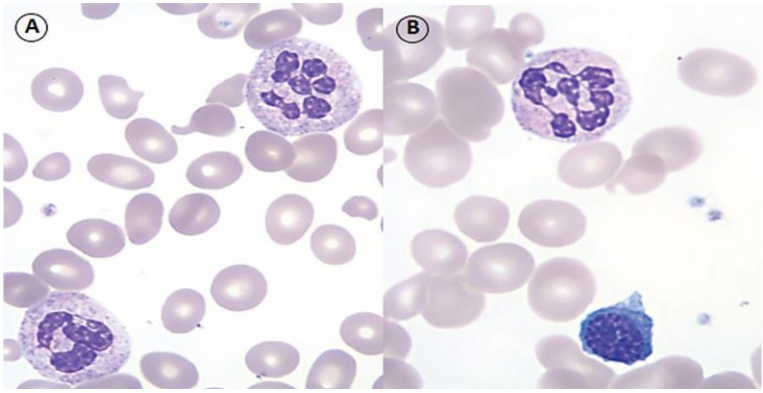


Figure 38: A, B: Two hypersegmented neutrophils (> 6 nuclear lobes) in peripheral blood smear (Wright-Giemsa, × 1000).

Basophil

Cell size varies between 10-14 microns. The nucleus/cytoplasm ratio is in favor of the cytoplasm. The nuclei are usually two-lobed, connected to each other by a thin chromatin filament. The nuclear chromatin network is dense and coarse. The cytoplasm is filled with black and coarse granules. Nuclei are seen in eosinophils, whereas nuclei attached to granules are usually absent in basophils. It is found in 0–1% of peripheral blood smear.

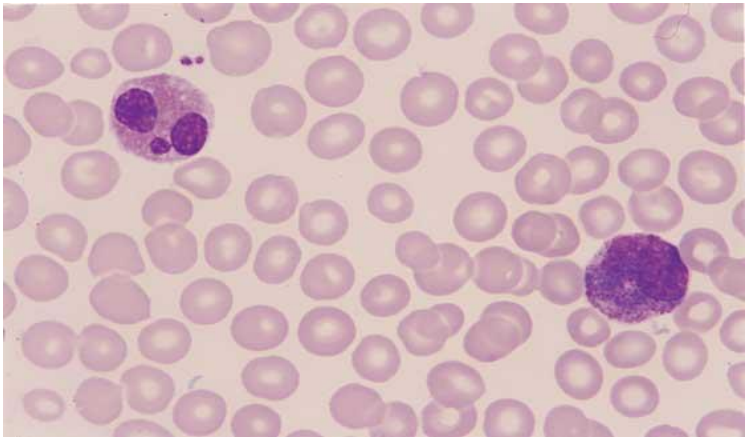


Figure 39: Basophil with large and dark colored granules in the cytoplasm of peripheral blood smear. The cell on the left is the eosinophil.

Eosinophil

Its size is between 12-17 microns. Cytoplasm is more in the nucleus/cytoplasm ratio. The nuclei are connected to each other by a thin chromatin thread and are in the form of two lobes. The nuclear chromatin structure is dense. The cytoplasm contains large granules of orange color. The core is visible. It is found in the range of 1–3% in peripheral blood smear. Its amount in the blood increases due to parasites, allergic reactions, skin diseases, drugs and chronic myeloproliferative disorders.

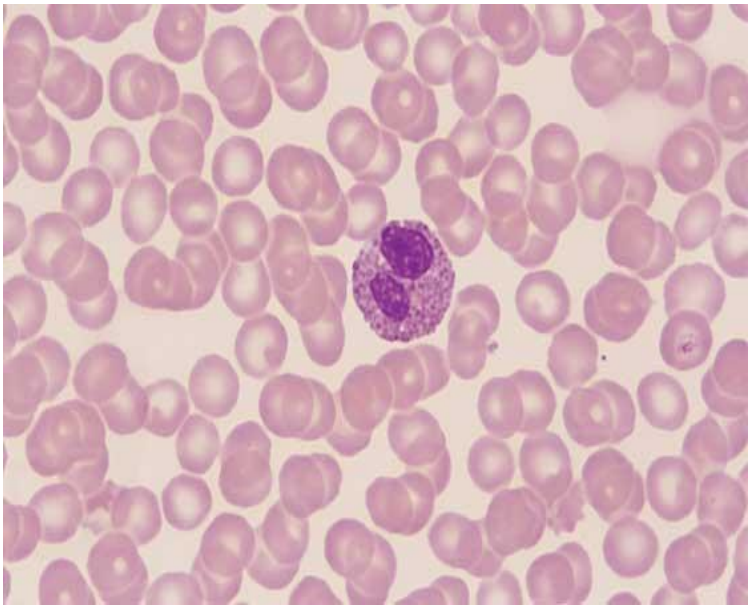


Figure 40: Peripheral blood smear shows an eosinophil with a two-lobed nucleus and large, orange-colored granules in the cytoplasm.

Platelets: Their job is to ensure blood clotting. Platelets in mammals do not contain nuclei, while those in fish, frogs, reptiles and birds contain nuclei. In mammals, they are not considered a true cell because they do not contain a nucleus. They exist in the form of cytoplasm particles. For this reason, platelets are also called platelets in mammals. They are the smallest dimensional structures of shaped

elements. Their diameter is around 2-3 microns. They are formed by the breakdown of megakaryocytes in the bone marrow. Platelets are around 200-400 thousand in 1 mm3 of blood. If their number falls below 200 thousand, it is called thrombocytopenia, and if it exceeds 400 thousand, it is called thrombocytosis.

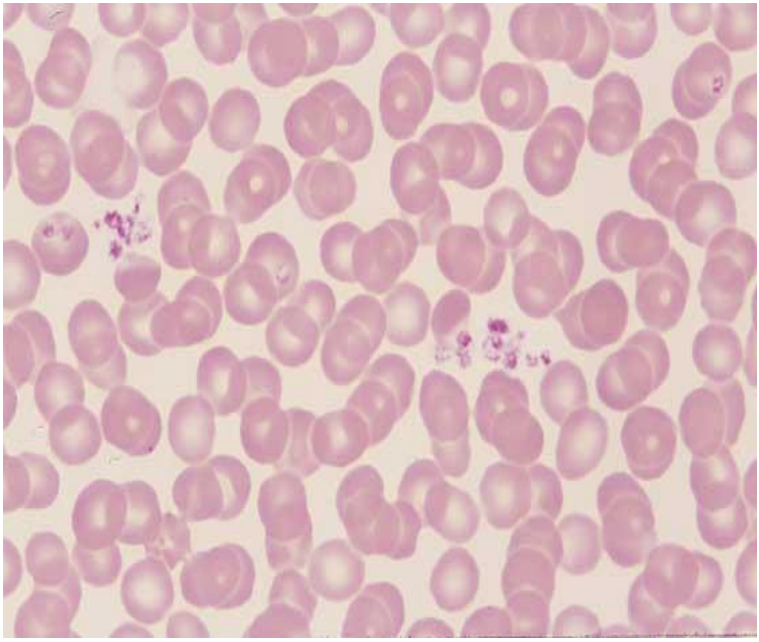


Figure 41: Clustered platelets are seen in the peripheral smear.

Amegakaryocytic Thrombocytopenia

It can be defined by the disappearance of platelets in the peripheral smear and the destruction of megakaryocytes in the bone marrow. It occurs congenital or acquired. The acquired type is defined by prolonged thrombocytopenia. It may occur due to alcohol, co-trimaxazol, phenylbutazone, chemical agents, parvovirus infections. Aplasia, acute leukemia, and myelodysplastic syndrome may occur in some patients. In peripheral smear, thrombocytopenia does not cause problems in other series in the bone marrow, whereas megakaryocytes are not seen.

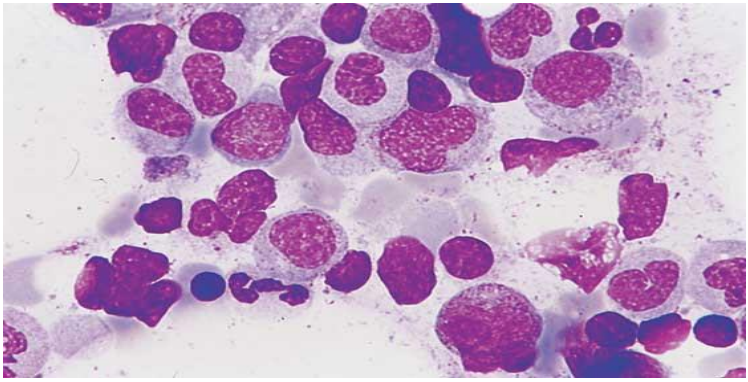


Figure 42: No megakaryocytes seen in bone marrow aspiration.

Glanzman's Thrombasthenia

It was described by Glanzman in 1918. It is characterized by aggregation of platelets despite normal platelet count and appearance. It occurs due to platelet glycoprotein IIb-IIIa deficiency or disorder. It is noteworthy that although the platelets are normal in the peripheral blood smears of the patients, they do not agglomerate. Since the same appearance can be seen in smears made from anticoagulant tubes, the patient's peripheral blood smear should be done from the fingertip.

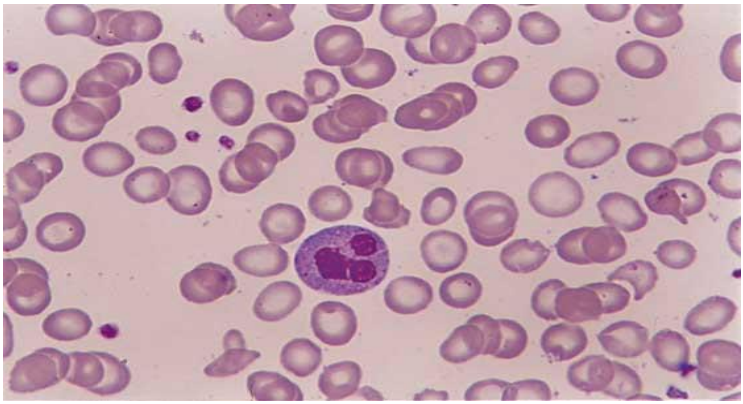


Figure 43: Large and non-aggregating platelets in peripheral blood smear, hypochromia is seen in erythrocytes.

Chronic Idiopathic Thrombocytopenic Purpura

MPV (mean platelet volume) has increased because there are large platelets due to platelet clogging in the peripheral blood. Large platelets due to accelerated thrombopoiesis are seen in peripheral smear. Hypochromic microcytic anemia may occur due to chronic blood loss. Leukocytosis is not usually seen except for acute bleeding. After steroid therapy, leukocytosis is seen, as leukocytes adhered to the vessel wall enter the circulation. Megakaryocytes may be increased in number in the bone marrow. There are non-platelet-producing megakaryocytes with mononuclear and basophilic cytoplasm.

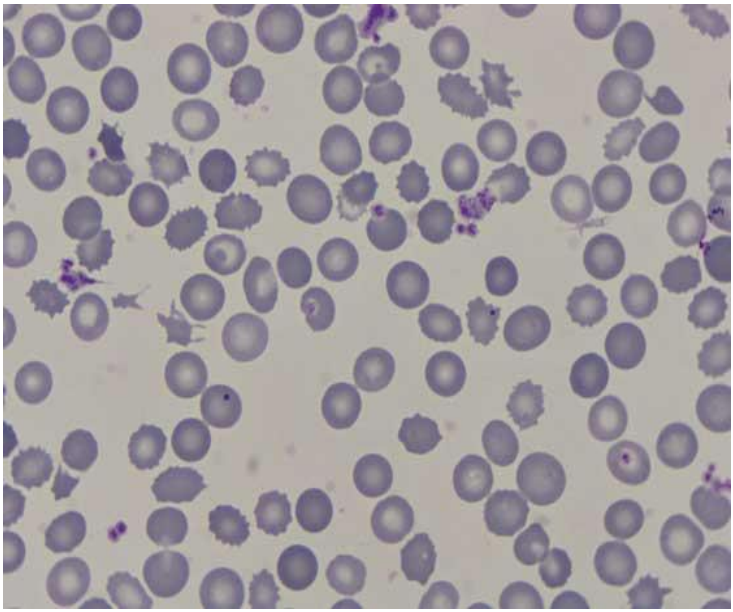


Figure 44: Peripheral smear of the patient with splenectomy shows sparse large platelets, anisocytosis, poikilocytosis and Howell Jolly bodies in erythrocytes.

There is an urgent need for many studies and evaluations to understand the pathogenesis of (COVID-19) emerging in 2019. Thrombotic complications seem to be very common, especially in patients diagnosed with COVID-19. It has been shown to contribute greatly to organ failure and death in particular. In addition, hemostatic abnormalities mimicking the diffuse intravascular

coagulopathy associated with sepsis have been observed in patients with severe COVID-19 detection, and when we consider the biggest difference, it has been suggested that the risk of thrombosis increases rather than bleeding. In addition to these features, it has not yet been demonstrated that coronavirus 2 infection, which shows severe acute respiratory syndrome, will contribute platelet function to the pathophysiology of COVID-19. In this study, altered platelet gene expression and functional responses in patients infected with SARS-CoV-2 are revealed. When we examined the RNA sequencing, it was determined that there was a significant change in the gene expression profile of circulating platelets from patients with COVID-19. In particular, the pathway analysis revealed that there are very serious changes in gene expression in pathways associated with protein ubiquitination, antigen presentation and mitochondrial dysfunction. It is a novel positive single-stranded RNA beta coronavirus in coronavirus 2 (SARS-CoV-2) patients showing severe acute respiratory syndrome and has been identified as the pathogen causing the ongoing coronavirus disease 2019 (COVID-19) pandemic. Although SARS-CoV-2 infection

is associated with the development of acute respiratory distress syndrome (ARDS), recent reports also describe patients who develop multiple organ failure and thrombosis, including myocardial infarction and ischemic stroke [31]. It has been shown that 20% to 30% of critically ill COVID-19 patients who experience thrombosis during SARS-CoV-2 infection, in which patients with cardiovascular problems and risk factors such as diabetes, obesity and hypertension, develop thrombotic complications, are below the risk table [32, 33]. Although thrombotic complications during infection are common in patients with SARS-CoV-2 disease, studies have shown that the pathological causes of thrombosis in COVID-19 remain unclear. In addition to the complications that occur in thrombosis and hemostasis, it has been suggested that platelets, inflammatory and immune processes are mediated as the root of the disease [34, 35]. Platelets with characteristics similar to cells involved in the human innate immune system have been demonstrated to express a wide array of receptors, including Toll-like receptors (TLRs), C-type lectin receptors, and nucleotide binding and

oligomerization domain-like receptors [36]. In general, platelets have been shown to support immune responses by directly interacting with neutrophils, monocytes and lymphocytes to further strengthen and support the immune response by releasing cytokines and antimicrobial peptides after detecting and detecting foreign pathogens that have entered [37]. Inflammatory and infectious diseases have often been suggested to be associated with a prothrombotic response called immunothrombosis, as platelet activation often occurs when platelets respond to invading pathogens. Immunothrombosis triggers immunological and hemostatic processes with very serious consequences. It has been demonstrated in studies that it provides support for very serious clinical outcomes such as vascular thrombosis, organ failure and death.

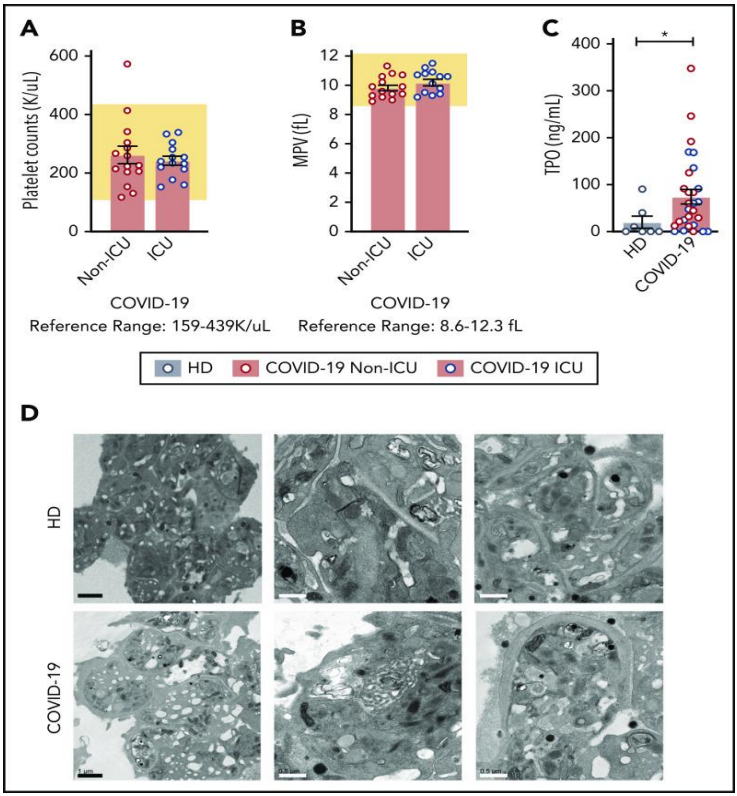


Figure 45: Platelet counts, MPV, and platelet morphology are normal in COVID-19 patients. (A) Platelet counts and (B) MPV, COVID-19 representation from non-ICU (red, n = 17) and ICU (blue, n = 12) patients is done. The reference range provided by ARUP is below the figure and is represented by the shaded region. (C) TPO levels were measured by enzyme-linked immunosorbent assay

(ELISA) in healthy donors (n = 7) and COVID-19 patients (non-ICU, n = 15; ICU, n = 14). Blue dots indicate ICU patients, red dots indicate non-ICU patients. (D) Platelets were isolated from healthy donors (n = 4; HD; top panel) and COVID-19 patients (n = 4; COVID-19; bottom panel) and adhered to Acylar coated with poly-lysine and imaged with a JEOL JEM-1011 electron microscope. Digital images were taken with the Side-mounted Advantage HR CCD camera. Lower power magnifications are provided on the left, with representative images from 2 individual donors or patients on the right at a higher magnification. Scale bars: black bars = 1 μm; white bars = 0.5 μm. *P <.05. K/uL denotes ×10 3/μL [38].

Duties of Blood

Transport: Transports matter between cells and the external environment.

- Nutrients
- Metabolites and enzymes
- waste materials

- O2 and CO2 breathing gases

- Hormones

- Transport of heat to surfaces where it will spread out

Homeostasis: Helps maintain pH with buffer systems. Optimum body temperature is 36-37oC, pH is between 7.35-7.45.

Defense: It creates an environment for phagocytizing foreign substances entering the body and rendering them harmless with antibodies. (White blood cells)

Stopping bleeding: It prevents blood loss by coagulating the blood with enzymes and platelets.

CONCLUSION

Many histological techniques are used in blood perperate smears. However, many techniques related to diseases are used and histopathology is evaluated clinically. The most commonly used histological stains in histopathology are Hemotoxylin, Wright-Giemsa, Giemsa and Diff-Quik stains. They are important in the diagnosis and evaluation of many diseases. In addition, electron microscopy is used in histopathological conditions.

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