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Review Article

Risk in Patients with Hematologic Diseases

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Abstract

Blood is present throughout the body, it is in constant movement through the blood vessels. It is in charge of dissimilar functions that play an important role in maintaining the homeostasis of the human body, transporting the necessary and essential resources for cells to function properly. Patients with blood disorders are frequent in daily dental consultations. Therefore, an exhaustive bibliographical review was carried out on the main risks and complications that can occur in these patients

Keywords: Blood; Homeostasis; Complications; Facial Injury; Oromaxillofacial Manifestation

Introduction

It is essential to maintain an adequate balance between the formed elements of the blood, when for any reason, the levels of these blood components are affected, different hematological noxas are established.

This chapter addresses the general aspects of the main diseases and hematological disorders, emphasizing the risks and complications that a professional in the branches of stomatology may face when a patient with these characteristics arrives [1,2].

Hematopoietic organs

Hematopoiesis (hemoblood poieis formation) is called the formation and development of blood cells. Cellular proliferation, differentiation, and maturation of hematopoietic tissue takes place in various organs, called hematopoietic: bone marrow, mononuclear phagocytic system, thymus, lymph nodes, spleen, and liver. The relationship between the bone marrow and hematopoiesis was discovered when it was found that the formation of blood follows a continuous and permanent process of supplying new formed elements to the blood circulation. The sites of hematopoiesis vary according to the developmental stage of the individual, hence the talk of the mesoblastic, hepatic, and medullary phases.

Erythrocytes

The average man has approximately 6 million erythrocytes per cubic millimeter of whole blood and the average woman somewhat less, around 5 million. Red blood cells, thanks to their hemoglobin content, transport oxygen to the tissues and remove carbon dioxide (CO2) from the tissues, which is then expired by the lungs. Disorders of the oxygen-carrying capacity are called anemias and may be due to a decrease in the number of erythrocytes, the size of each cell, or its hemoglobin content. Most disorders that affect red blood cells are anemias [1-3].

Anemia

Concept

Anemia is the name given to the decreased oxygen-carrying capacity of erythrocytes. It may result from a reduction in the number of erythrocytes, a decrease in their size, or a decrease in their hemoglobin content. It is defined as a hemoglobin (Hb) value less than 12 g/dl in women and less than 13 g/dl in men.

These alterations may be due to various etiological factors

- Excessive blood loss from trauma or internal bleeding, or from spontaneous hemolysis, which may be the consequence of autoimmune mechanisms through which antibodies bind to red blood cells, fix complement, and lyse them.
- Genetic diseases with alterations in hemoglobin, causing pathological cell morphology that predisposes to cell lysis.
- Nutritional deficiencies with insufficient dietary intake or lack of intestinal absorption of erythrocyte precursor substances.

In the laboratory, anemia is assessed

- Performing an erythrocyte count.
- Determining the total cell volume (hematocrit)
- Quantifying the amount of hemoglobin.
    - These three parameters are combined, giving rise to the erythrocyte indices. These indices help determine the

size and hemoglobin content of each red blood cell. Even if the total red blood cell count is within normal range, the patient may experience decreased oxygen-carrying capacity if the cells are too small. In this case, the hematocrit would be decreased. Even if the number of cells is normal, it will indicate a decrease in the total volume or mass in the blood sample. Anemia characterized by decreased red cell volume is called microcytic anemia.

- It may also happen that the cells are of normal size, but contain an insufficient amount of hemoglobin, so the patient will be anemic. Anemia secondary to decreased hemoglobin content in cells of normal size is called hypochromic anemia. If the total number of red blood cells decreases and the bone marrow tries to compensate by making larger cells with a higher concentration of hemoglobin, the anemia is classified as macrocytic hyperchromic anemia.

Microcytic anemia

- Iron deficiency anemia

Concept

- Iron deficiency anemia is a common type of anemia, as the name suggests, iron deficiency anemia is due to a lack of iron. Without the necessary iron, the body cannot produce a sufficient amount of hemoglobin, a substance present in red blood cells that allows them to carry oxygen.
- Etiology

Causes of iron deficiency anemia include

Loss of blood. Blood contains iron within the red blood cells. If you lose blood, you lose some iron. Women with heavy periods are at risk of iron deficiency anemia because they lose blood during the menstrual period. Slow, continuous blood loss within the body (for example, from a peptic ulcer, hiatal hernia, colon polyp, or colorectal cancer) can cause iron deficiency anemia. Gastrointestinal bleeding can result from the regular use of some over-the-counter pain relievers, especially aspirin.

- Lack of iron in your diet. The body regularly gets iron from the food you eat. If you consume too little iron, over time you can become iron deficient. Some examples of iron-rich foods are meats, eggs, green leafy vegetables, and iron-fortified foods. For good growth and development, infants and children also need dietary iron [4].
- Inability to absorb iron. Iron from food is absorbed in the small intestine and passes into the bloodstream. Intestinal disorders that affect the intestine's ability to absorb nutrients from digested food, such as celiac disease, can cause iron deficiency anemia. If you've had an intestinal bypass or had part of your small intestine surgically removed, your ability to absorb iron and other nutrients may have been affected.
- Pregnancy. If they do not take iron supplements, many pregnant women could develop iron deficiency anemia because their iron stores have to meet the demand for increased blood volume and provide hemoglobin for the developing fetus.

Clinical picture

Initially, iron deficiency anemia may be so mild that it goes unnoticed. But as the body becomes more deficient in iron and the anemia worsens, the signs and symptoms intensify.

Signs and symptoms of iron deficiency anemia may include

- Extreme fatigue
- Weakness
- Pale skin
- Chest pain, rapid heartbeat, or shortness of breath
- Headache, dizziness or vertigo
- Cold hands and feet
- Swelling or pain in the tongue
- Brittle nails
- Unusual cravings for non-nutritive substances, such as ice, dirt, or starch.
- Lack of appetite, especially in babies and children with iron deficiency anemia.

Thalassemia (Mediterranean Anemia)

Concept

It is an inherited blood disorder that occurs when the body does not produce enough hemoglobin.

Etiology

Thalassemia is caused by mutations in the deoxyribonucleic acid (DNA) of cells that produce hemoglobin, the substance in red blood cells that carries oxygen throughout the body. Mutations associated with thalassemia are passed from parent to child.

Hemoglobin molecules are made up of chains called alpha and beta chains, which can be affected by mutations. In thalassemia, the production of alpha or beta chains is reduced, leading to alpha-thalassemia or beta-thalassemia.

In alpha thalassemia, the severity of thalassemia you have depends on the number of gene mutations you inherit from your parents. The more mutated the genes are, the more severe the thalassemia will be. In beta thalassemia, the severity of the thalassemia depends on the part of the hemoglobin molecule that is affected.

Alpha-thalassemia

Four genes are involved in the formation of the alpha hemoglobin chain. You have two of each parent. If inherited

- One mutated gene, will not have signs or symptoms of thalassemia. But they will be carriers of the disease and can pass it on to their children.
- Two mutated genes, your signs and symptoms of thalassemia will be mild. This condition could be called characteristic of alpha-thalassemia.
- Three mutated genes, your signs and symptoms will be moderate to severe.

The inheritance of four mutated genes is rare and usually results in fetal or intrauterine death. Babies born with this condition often die shortly after birth or require lifelong transfusion therapy. In rare cases, a child born with this condition may be treated with transfusions and a stem cell transplant.

Betatalasemia

Two genes are involved in the formation of the beta hemoglobin chain. They receive one from each of their parents. If inherited

- A mutated gene, will have mild signs and symptoms. This condition is called thalassemia minor or beta thalassemia.
- Two mutated genes, your signs and symptoms will be moderate to severe. This condition is called thalassemia major or Cooley's anemia.

Babies born with two defective beta-hemoglobin genes are generally healthy at birth, but develop signs and symptoms within the first two years of life. A milder form, called thalassemia intermedia, can also result from two mutated genes.

Clinical picture

There are several types of thalassemia. The signs and symptoms you have depend on the type and severity of the condition [1,2,5].

Signs and symptoms of thalassemia may include the following:

- Fatigue
- Weakness
- Pale or yellowish skin
- Facial bone deformities
- Slow growth
- Abdominal swelling
- Dark urine
-

Some babies show signs and symptoms of thalassemia at birth; others develop them during the first two years of life. Some people who have only one affected hemoglobin gene do not have symptoms of thalassemia.

Macrocytic anemias

Pernicious anemia

Pernicious anemia develops when the body is unable to absorb the vitamin B12 it needs from food due to a lack of a protein, called intrinsic factor, produced by the stomach. Intrinsic factor is required for the absorption of vitamin B12. Pernicious anemia is often associated with an autoimmune attack of stomach parietal cells and/or intrinsic factor.

Etiology

There are many possible causes of pernicious anemia.

- Vitamin B12 deficiency
- Atrophic gastritis
- Alteration in the cells that produce both intrinsic factor and hydrochloric acid in the stomach. Intrinsic factor is a protein necessary for the absorption of vitamin B12.
- Genetics

A risk factor is something that increases your chance of getting a disease or condition. The following factors increase the chances of developing pernicious anemia

Autoimmune disorders and other conditions, such as

- Diabetes type 1
- Addison's disease
- Graves' disease
- Myasthenia gravis
- Secondary amenorrhea
- Hypoparathyroidism
- Hypopituitarism
- Testicular dysfunction
- Chronic thyroiditis
- Vitiligo
- Idiopathic adrenocortical insufficiency
- Ancestry: Northern European or Scandinavian
- Age: more than 50 years
- Sjogren's syndrome
- Celiac

Clinical picture

The symptoms of pernicious anemia vary from person to person. Symptoms can change or get worse over time. They may include

- Stinging and stinging sensation in the feet or hands
- Alternating constipation and diarrhea
- Burning sensation on the tongue or a smooth, red tongue
- Substantial weight loss
- Inability to distinguish the colors blue and yellow.

- Fatigue
- Paleness
- Loss of appetite
- Altered sense of taste
- Confusion
- Depression
- Impaired sense of balance, especially in the dark
- Ringing in the ears
- Chapped lips
- Fever
- Inability to feel vibration in the feet or legs
- Dizziness when changing to standing up
- Fast heartbeat

Megaloblastic anemia

Concept

Megaloblastic anemia is a macrocytic anemia that results from inhibition of DNA synthesis in the production of red blood cells. When DNA synthesis stops, the cell cycle is unable to transition from the G2 phase of growth to the mitosis phase. This leads to the cell continuing to grow without dividing, resulting in macrocytosis.

This defect in DNA synthesis is frequently due to hypovitaminosis, specifically a deficiency of vitamin B12 or folic acid (vitamin B9). The term megaloblastic refers to the large size (megalo) of the precursor cells (blasts) of the bone marrow (including red blood cells), because cytoplasmic maturation is greater than nuclear [2,6].

Etiology

The main and most frequent causes of megaloblastic anemias are

- Diseases of the digestive system
- Drug-induced folic acid deficiency, this can usually be treated with a dietary supplement.

Folic acid deficiency

- Excess demand: chronic hemolysis, pregnancy or growth.
- Malabsorption: drugs, alcoholism, chronic enteritis
- Ill-balanced vegetarian and/or vegan diets, without B9 supplements or foods without B9 fortification

Vitamin B12 deficiency

- Pernicious anemia
- Gastrectomy
- Resection of the terminal ileum (blind loop syndrome)
- Fish tapeworm infestation
- Family: juvenile or hereditary
- Intestinal hypomotility (amyloidosis)
- Unbalanced vegetarian and/or vegan diets without B12 supplements or foods without B12 fortification
- Copper deficiency, for example, as a result of a high intake of zinc found in dental fixative creams, has been the cause of this anemia.

Clinical picture

The symptoms vary depending on the factor that causes the anemia, in general it is common to see:

Loss of appetite

- Paresthesias (tingling) and numbness of hands and feet, vertigo, irritability
- Paleness or other changes in skin coloration
- Tiredness, weakness, fatigue
- Headaches
- Ulcers in the mouth and on the tongue
- Loss of concentration
- Diarrhea or constipation
- Shortness of breath, especially during exercise
- Normocytic anemias

Hemolytic anemia

Concept

- It is anemia resulting from the premature destruction of red blood cells within the blood circulation, without the bone marrow producing enough red blood cells to replace those destroyed.
- They are classified in
- Hemolysis (rupture of red blood cells) within the spleen (extravascular hemolysis). It is usually due to defects in the manufacture of red blood cells. Because red blood cells are defective, they are destroyed in the spleen, the organ where red blood cells are destroyed when they age. Manufacturing defects can be located in the red blood cell membrane or in its hemoglobin. Sometimes the problem is not in the red blood cell, but there are antibodies that attack the own red blood cells, which is called autoimmune hemolytic anemia. This attack leads to red blood cells with antibodies attached to their surface being destroyed as they pass through the spleen.
- Hemolysis in the blood circulation itself (intravascular hemolysis). It is usually due to the destruction of red blood cells as a result of infections, medications, metal prostheses in the heart, or a deficiency of glucose 6 phosphate dehydrogenase, an enzyme that is not very useful under normal circumstances but that in stressful situations. (infections, inflammations, etc.) protects the red blood cell from being destroyed. If this enzyme is missing, red blood cells are destroyed by infections or other diseases [7].

Etiology

Hemolytic anemias can be divided into

Hereditary anemia, that is, patients were born with a genetic defect that favors the destruction of red blood cells. This defect can be:

- A problem in the manufacture of hemoglobin: includes thalassemia, sickle cell anemia, and other less frequent diseases.
- Alterations in the manufacture of the membrane (cover) of the red blood cell. Includes spherocytosis, elliptocytosis and other diseases. The red blood cell membrane is abnormal and these cells live for a shorter time, usually destroying themselves inside the spleen. They can be mild forms that are diagnosed in adulthood or severe forms already identified in childhood.
- Defects in enzymes inside the red blood cell. The most common is glucose 6 phosphate dehydrogenase defect. It is an X-linked disease (males suffer from it more frequently) that usually occurs without symptoms. When there are symptoms, they consist of jaundice at birth (neonatal jaundice) or episodes of hemolytic anemia related to the consumption of broad beans, infections or taking some medications.

Acquired hemolytic anemias. You are not born with them, but are due to some problem acquired after birth. They may be due to

- Mechanical destruction of red blood cells, for example, due to metallic heart prostheses or haemolysis from a march (race, marathon, etc.) or walking or dancing barefoot for a long time, when the red blood cells that travel through the sole of the foot break.
- For medications. It can occur even in people without glucose 6 phosphate dehydrogenase deficiency. In general it is rare. Sometimes medications can cause allergic reactions that favor hemolysis, such as some penicillins.
- Infections that destroy red blood cells, such as malaria.
- Of autoimmune cause. They are the most frequent cause of acquired hemolytic anemias in Western countries. They occur because, for an unknown cause, antibodies are created against red blood cells (your own defenses attack your red blood cells), which leads to their destruction, generally in the spleen. It is usually associated with other autoimmune diseases such as lupus erythematosus, etc.
- Paroxysmal nocturnal hemoglobinuria.

Clinical picture

The symptoms of anemia depend on the rapidity of its onset and its cause. Hemoglobin is the protein that carries oxygen to all parts of the body, so if it is missing it usually appears

- Fatigue
- Feeling of shortness of breath (dyspnea).
- Exhausted
- Feeling short of breath
- Heart failure
- Red urine.

The most chronic anemias may not produce any symptoms and be a casual finding when performing an analysis for any reason. If they are very important, they can produce

- Tiredness, shortness of breath, paleness and heart failure, all slowly and progressively onset [2,3,8].

Sickle cell anemia (sickle cell, siklemia)

Concept

Sickle cell disease is part of a group of inherited disorders known as "sickle cell disease." It affects the shape of the red blood cells that carry oxygen throughout the body.

Normally, red blood cells are round and flexible to move easily through blood vessels. In sickle cell anemia, some red blood cells are shaped like a sickle or crescent. These blood cells also become stiff and sticky, which can slow or block blood flow.

Etiology

A change in the gene that tells the body to make the iron-rich compound in red blood cells called hemoglobin causes sickle cell anemia. Hemoglobin allows red blood cells to carry oxygen from the lungs throughout the body. The hemoglobin associated with sickle cell disease causes the red blood cells to become stiff, sticky, and misshapen.

For a child to have the condition, both the mother and father must carry one copy of the sickle cell gene, also known as sickle cell trait, and pass both copies of the altered form to the child.

If only one parent passes the sickle cell gene to the child, that child will have the sickle cell genetic trait. With one normal hemoglobin gene and one altered form of the gene, people with sickle cell trait make both normal hemoglobin and sickle cell hemoglobin.

Their blood may contain some sickle cells, but they usually have no symptoms. However, they are carriers of the disease, which means they can pass the gene on to their children.

Clinical picture

The signs and symptoms of sickle cell anemia usually appear around 6 months of age. They vary from person to person and can change over time. Signs and symptoms may include the following

- Anemia. Sickle cells break easily and die. Red blood cells typically live for about 120 days before they need to be replaced. However, sickle cells usually die within 10 to 20 days, resulting in a shortage of red blood cells (anemia). Without enough red blood cells, the body can't get enough oxygen, and this causes fatigue.
- Episodes of pain. Periodic episodes of extreme pain, called pain crises, are a major symptom of sickle cell disease. Pain occurs when sickle-shaped red blood cells block blood flow in small blood vessels in the chest, abdomen, and joints.

- The pain varies in intensity and can last from a few hours to a few days. Some people only have a few pain crises a year. Others have a dozen a year or more. A severe pain crisis requires hospitalization.
- Some teens and adults with sickle cell disease also have chronic pain, which can be the result of bone and joint damage, ulcers, and other causes.
- Swelling of hands and feet. The inflammatory process is a consequence of sickle-shaped red blood cells blocking blood circulation in the hands and feet.
- Frequent infections. Sickle cells can damage the spleen, increasing its vulnerability to infection. Babies and children with sickle cell disease are usually vaccinated and given antibiotics to prevent life-threatening infections, such as pneumonia [9].
- Delayed growth or puberty. Red blood cells provide the body with the oxygen and nutrients necessary for growth. A shortage of healthy red blood cells can slow growth in babies and children, and delay puberty in teens.
- Vision problems. The tiny blood vessels that supply the eyes can become clogged with sickle cells. This can damage the retina, the part of the eye that processes visual images, and cause vision problems.

Aplastic anemia

Concept

- Aplastic anemia (AP) is a condition that occurs when the body stops making the necessary number of new blood cells. The condition causes fatigue and increases the susceptibility to infections and uncontrolled bleeding.
- PA is a rare and serious condition, which can develop at any age. It can happen suddenly, or it can come on slowly and get worse over time. It can be mild or severe.

Etiology

- Stem cells in the bone marrow make blood cells: red blood cells, white blood cells, and platelets. In AP, the stem cells are damaged. As a result, the bone marrow is aplastic or contains few blood cells (hypoplastic).

The most common cause of PA is when the immune system attacks stem cells in the bone marrow. These are other factors that can damage the bone marrow and affect the production of blood cells

- Radiation and chemotherapy treatments. While these cancer therapies kill cancer cells, they can also harm healthy cells, including stem cells in the bone marrow. Aplastic anemia can be a temporary side effect of these treatments.
- Exposure to toxic chemicals. Toxic chemicals, such as some used in pesticides and insecticides, and benzene, an ingredient in gasoline, have been linked to aplastic anemia. This type of anemia may improve if repeated exposure to the chemicals that caused the disease is avoided.
- Use of certain medications. Some drugs, such as those used to treat rheumatoid arthritis and some antibiotics, can cause PA.
- Autoimmune disorders. An autoimmune disorder, in which the immune system attacks healthy cells, can affect stem cells in the bone marrow.
- A viral infection. Viral infections that affect the bone marrow may play a role in the development of PA. Viruses that have been linked to aplastic anemia include hepatitis virus, Epstein-Barr virus, cytomegalovirus, parvovirus B19, and HIV.
- Pregnancy. The immune system can attack the bone marrow during pregnancy.
- Unknown factors. In many cases, doctors cannot identify the cause of aplastic anemia (idiopathic aplastic anemia).
- Connections to other rare disorders: Some people with aplastic anemia also have a very rare disorder known as paroxysmal nocturnal hemoglobinuria, which causes red blood cells to break down too quickly. This condition can cause PA, or this can develop into paroxysmal nocturnal hemoglobinuria.
- Fanconi anemia is a very rare hereditary disease that causes PA. Children born with this disease are often smaller than average and have birth defects, such as underdeveloped limbs. The disease is diagnosed with a blood test.

Clinical picture

- PA may have no symptoms. When they do occur, signs and symptoms may include:
- Fatigue
- Dyspnea
- Fast or irregular heart rate
- Pale skin
- Frequent or prolonged infections
- Bruising without apparent cause or that appears easily
- Bleeding from the nose or gums
- Prolonged bleeding from cuts
- Acne
- Dizziness
- Headache
- Fever
- PA can be short-lived or chronic. It can be serious and even deadly.

Risk and complications in Stomatology with the anemic patient

- Stomatology as a discipline of Medical Sciences constitutes a vitally important specialty that provides treatment to patients with various diseases. Among these, hematological alterations stand out which, due to their generally chronic course, their patients require periodic dental care.

- Hematological diseases constitute a reason for consultation in primary and secondary health areas. On various occasions, they present as a stomatological emergency, so the professional must know how to relate certain clinical manifestations with said pathological lesions. Through a correct anamnesis, clinical and complementary examination, you must diagnose and apply an adequate treatment that responds to the needs of the disease of the patient you are facing, and have knowledge about the risks to which these patients are exposed in the care stomatology.
- The main erythrocyte disorders associated with oral problems are those related to the anemic syndrome in which a series of effects caused by hypoxia occur due to a drop in hemoglobin. This hinders the distribution of oxygen, and the compensatory mechanisms of the organism. The patient with anemic syndrome requires urgent medical attention, so the dental consultation must be postponed until the patient is stable, if urgent treatment is required it must be palliative, do not perform any surgical treatment due to blood loss, in case of It will be necessary to transfuse a red blood cell packet after consultation with a hematologist.

The stomatological management of the patient with anemia consists of several guidelines due to the high risk that these patients present, among the measures are:

- The patient with anemia should receive medical attention regardless of the fact that in the dental office they may present reparative and infectious disorders [1,2].
- In patients with undiagnosed anemia, dental treatment should be postponed and managed only with palliative care.
- In patients with chronic or borderline anemia or kidney patients who tolerate low hemoglobin levels well, non-invasive surgical procedures, prophylaxis, fluoride, sealants, prostheses can be performed, although they must be under medical supervision.
- Surgical procedures should be postponed, since they would imply blood loss, which translates into less oxygenation, which compromises healing, which can lead to post-surgical bleeding, as well as added infections.
- In urgent cases, request consultation with the treating physician to assess a possible transfusion of concentrated erythrocytes.
- Contraindicated procedures under general inhalation anesthesia due to the risk of hypoxia and acidosis, since anesthetic gases are related to hemoglobin and displace oxygen.
- Patients with a history of anemia or undergoing treatment should be given short appointments and preferably in the morning.
- In patients with aplastic anemia, platelets and white blood cells are also affected, so hemorrhagic events must be avoided and, in case of necessary care, antibiotic prophylaxis may be required.
- Patients with anemia usually present burning, tenderness, ulcerations and pain, so these should be treated palliatively (warm saline or bicarbonated water mouthwashes to reduce discomfort and clean ulcers, topical anesthetics or sedatives; avoiding the use of prostheses and orthopedic appliances that would cause local irritation until the patient is fully controlled. To avoid infections, local antibacterials or antiseptic rinses that do not irritate the mucosa are used, avoiding iodinated or alcohol-based products. In case of cheilitis, use of topical antifungals.
- Antibacterial prophylaxis is important in these patients when a surgical procedure is to be performed, in addition, the risks of necrosis, infection, and wound dehiscence must be explained to the patient and family members. There are very few patients who can adequately assume a bone graft, with these systemic characteristics, free grafts have a high percentage of failures.
- In these patients, in addition, great delicacy must be exercised when applying a local anesthetic, and if possible avoid excessive use of vasoconstrictors [8,9].

Summary table of the main risks and complications of the anemic patient in Stomatology	
Own the disease	Proper of the proceeding
Damage to periodontal tissues	Necrosis at the anesthetic puncture site.
Damage to the oral mucosa	Flap necrosis
Involvement of the specialized mucosa of the tongue	Free graft necrosis
Infection of the skin and other tissues	Bleeding in the PA
Bleeding at minimal stimulation or spontaneous	Infection
Damage to multiple organs	Delayed healing in soft tissues
Prostration	Delayed healing in hard tissues
Growth disturbances in pediatric patients	Nonunion
Imbalance in the oral flora	dry socket
Death	

Table 1

Haemostasis disorders

Hemostasis disorders are a group of conditions in which there is a problem with the body's blood clotting process. These disorders can lead to heavy and prolonged bleeding after an injury. Bleeding can also start spontaneously.

Specific bleeding disorders include

- Acquired defects of platelet function
- Congenital defects of platelet function

- Disseminated intravascular coagulation (DIC)
- Prothrombin deficiency
- Factor V deficiency
- Factor VII deficiency
- Factor X deficiency
- Factor XI deficiency (hemophilia C)
- Glanzmann's disease
- Hemophilia A
- Hemophilia B
- Idiopathic thrombocytopenic purpura (ITP)
- Von Willebrand disease (types I, II and III)

Etiology

Normal blood clotting involves blood components called platelets and up to 20 different plasma proteins. These proteins are known as coagulation factors or blood clotting factors. These factors interact with other chemicals to form a substance that stops bleeding called fibrin.

Problems can occur when certain clotting factors are missing or very low. Bleeding problems can range from mild to severe.

Some bleeding disorders are present from birth and are passed from parent to child (inherited). Others are developed by

- Conditions such as vitamin K deficiency and severe liver disease

Treatments such as the use of medicines to stop blood clots (anticoagulants) or long-term use of antibiotics

- Bleeding disorders can also result from the number and function of the blood cells that promote blood clotting (platelets). These disorders can also run in families or develop later (acquired). Side effects of certain medications often lead to the acquired forms [9,10].

Acquired Defect of Platelet Function (Acquired qualitative platelet disorders; Acquired disorders of platelet function)

Concept

- Acquired defects in platelet function are conditions that cause blood elements needed for clotting called platelets to not work properly. The term acquired means that these conditions are not present at birth.
- Normal platelet values range in neonates and adults from 150,000 to 450,000 platelets/µL.

Etiology

- Platelet disorders can affect the number of platelets, their proper function, or both. A platelet disorder affects normal blood clotting. Disorders that can cause platelet function problems include:
- Idiopathic thrombocytopenic purpura (bleeding disorder in which the immune system destroys platelets)
- Chronic myelogenous leukemia (blood cancer that starts within the bone marrow)
- Multiple myeloma (blood cancer that begins in the plasma of bone marrow cells)
- Primary myelofibrosis (a disorder of the bone marrow in which the bone marrow is replaced by fibrous scar tissue)
- Polycythemia vera (disease of the bone marrow that causes an abnormal increase in the number of blood cells)
- Primary thrombocytopenia (a bone marrow disorder in which the bone marrow makes too many platelets)
- Thrombotic thrombocytopenic purpura (blood disorder that causes clots to form in small blood vessels)
- Other causes include:
- Renal insufficiency
- Medications such as acetylsalicylic acid (aspirin), ibuprofen, other anti-inflammatories, penicillin, phenothiazines, and prednisone (after long-term use).
- clinical picture
- Symptoms may include any of the following:
- Heavy or prolonged menstrual periods (more than 5 days per menstrual period)
- Abnormal vaginal bleeding
- Bleeding in the urine
- Subcutaneous bleeding
- Easy bruising or small red spots on the skin
- Gastrointestinal bleeding resulting in bloody, black, or tarry stools; or vomit with blood or material that looks like coffee grounds
- Nosebleeds (Epistase)

Congenital Defects of Platelet Function

Concept

- These are conditions that cause reduced platelet function. Congenital means present from birth.

Etiology

- People with these disorders usually have a family history of a bleeding disorder, such as:
- Bernard-Soulier syndrome occurs when platelets lack a substance that sticks them to the walls of blood vessels. These are generally large and of small quantity. This disorder that can cause heavy bleeding.
- Glanzmann's thrombasthenia is a condition caused by a lack of a protein required for platelets to clump together. Platelets are generally of normal size and number. It can also cause heavy bleeding.
- Intraplatelet storage defect disorder (also called platelet secretion disorder) is due to one of several defects or abnormalities that cause easy bruising or bleeding and is caused by defective storage of substances within platelets. These substances are generally secreted to help platelets function properly.

Clinical picture

Symptoms may include any of the following

- Bleeding (hemorrhage) during and after surgery.
- Bleeding gums
- Tendency to bruise or bruise
    - Heavy menstrual periods
    - Nosebleed (epistaxis)
    - Prolonged bleeding with small lesions

Disseminated intravascular coagulation

Concept

Disseminated intravascular coagulation (DIC) or consumption coagulopathy is defined as a disorder secondary to an underlying process, which can be acute or chronic and is characterized by abnormal activation of the coagulation mechanism, thrombin generation at the microcirculation level, consumption of platelets and coagulation factors and activation of the fibrinolysis mechanism that lead the patient to a critical state in which microvascular thrombosis and clinical hemorrhage coexist.

Etiology

- **Infections**: the most frequent are those caused by gram-negative germs, especially those of intestinal origin (Escherichia coli, Salmonella, Klebsiella, Proteus, etc.). These cover 70% of cases.
- **Obstetric accidents:** placenta previa, retained dead fetus, placental abruption, amniotic fluid embolism.
- **Cancer:** any type of cancer is capable of generating a DIC, however, the most common are those of the digestive tract, leukemias, especially acute promyelocytic leukemia, and some tumors of the central nervous system [1,2].
- **Vascular abnormalities:** Kasabach-Merritt syndrome, vascular malformations, and aortic aneurysm.
- **Others:** acid base imbalance, burns, severe haemolysis, allergic/toxic reactions (snake bite), severe immune reactions (transfusion reaction) etc.

Clinical picture

- The main manifestation is bleeding. The most common site of bleeding is the skin (petechiae, ecchymosis, and superficial bruising).
- Bleeding tendency (venipuncture sites, when applying the sphygmomanometer cuff or tourniquets for taking laboratory tests)
- In addition to bleeding, the signs and symptoms of the triggering disease are present and can be found.

Etiology

- **Infections:** the most frequent are those caused by gram-negative germs, especially those of intestinal origin (Escherichia coli, Salmonella, Klebsiella, Proteus, etc.). These cover 70% of cases.
- **Obstetric accidents:** placenta previa, retained dead fetus, placental abruption, amniotic fluid embolism.
- **Cancer:** any type of cancer is capable of generating a DIC, however, the most common are those of the digestive tract, leukemias, especially acute promyelocytic leukemia, and some tumors of the central nervous system.
- **Vascular abnormalities:** Kasabach-Merritt syndrome, vascular malformations, and aortic aneurysm.
- **Others:** acid base imbalance, burns, severe haemolysis, allergic/toxic reactions (snake bite), severe immune reactions (transfusion reaction) etc.

Clinical picture

- The main manifestation is bleeding. The most common site of bleeding is the skin (petechiae, ecchymosis, and superficial bruising).
- Bleeding tendency (venipuncture sites, when applying the sphygmomanometer cuff or tourniquets for taking laboratory tests)

In addition to bleeding, the signs and symptoms of the triggering disease are present and can be found.

Prothrombin deficiency can also be caused by another condition or the use of certain medications. This is called acquired prothrombin deficiency. It can be caused by

- Vitamin K deficiency (some babies are born with vitamin K deficiency)
- Severe liver disease
- Use of drugs to prevent clotting (anticoagulants such as warfarin)

Clinical picture

- Symptoms may include any of the following:
- Abnormal bleeding after delivery
- Heavy menstrual bleeding
- Bleeding after surgery
- Bleeding after trauma
- Propensity to bruise
- Nosebleeds that do not stop easily
- Bleeding from the umbilical cord at birth

Coagulation Factor V Deficiency (labile factor)

Concept

- Congenital factor V deficiency is a coagulopathy that is transmitted in an autosomal recessive manner and whose preva-

lence is 1:1,000,000. Heterozygotes for this disease are usually asymptomatic. The responsible gene is on the long arm of chromosome 1 [1,2,10,11].

Etiology

- Congenital factor V deficiency is caused by mutations in the F5 gene (1q23), which controls the production of plasma factor V.

Clinical picture

Symptoms of factor V deficiency are usually mild, and children with severe factor V deficiency may have

- Bleeding at a very young age. Brain and spinal cord hemorrhages.
- Epistaxis
- Bruising, menorrhagia, bleeding after surgery, childbirth or trauma.

Other less common symptoms include

- Gastrointestinal and muscle bleeding, hemarthrosis, and central nervous system (brain and spinal cord) bleeding.

Factor VII deficiency

Concept

- Factor VII deficiency is a rare hemorrhagic disease, caused by the decrease or absence of this coagulation factor. Said factor is a glycoprotein synthesized by the liver and dependent on vitamin K. It is transmitted in an autosomal recessive manner.

Etiology

- The disease is caused by mutations in the F7 gene (13q34), which codes for factor VII. Homozygous or compound heterozygous individuals usually develop a hemorrhagic syndrome; heterozygous patients usually remain asymptomatic. The proximity and involvement with the F10 gene (13q34) could also be the cause of combined deficits.

Clinical picture

The clinical expression is highly variable and no consistent relationship has been found between the severity of the hemorrhagic syndrome and the residual levels of Factor VII activity. The clinical picture can be very serious with

- Early onset of intracerebral hemorrhages or recurrent hemarthrosis; or, conversely, moderate with cutaneous-mucosal bleeding (epistaxis, menorrhagia)
- Bleeding caused by surgical interventions [1,2,12].

Factor X deficiency (Stuart-Power factor)

Concept

A rare hereditary bleeding disorder with decreased factor X (FX) antigen or activity and characterized by mild to severe bleeding manifestations.

Etiology

Factor X deficiency is often caused by an inherited defect in the factor X gene (13q34). Coagulation factor X is synthesized by the liver and depends on vitamin K. It is involved in both the intrinsic and extrinsic pathways of coagulation and is the first enzyme of the common pathway.

Congenital factor X deficiency is due to a reduction in factor X activity and/or antigen. It is transmitted in an autosomal recessive manner, therefore it affects women and men equally, and the responsible gene is found in the long arm of the factor X. chromosome 13. The prevalence is estimated at 1/500,000.

Factor X deficiency can also be due to another condition or the use of medications, then called acquired factor X deficiency. It can be caused by severe liver disease, amyloidosis, a lack of vitamin K, or the use of anticoagulant drugs.

Clinical picture

The lower the concentration of factor X in the blood, the greater the frequency and/or severity of the symptoms.

- Serious bleeding from the umbilical cord
- Recurrent epistaxis
- Soft tissue bleeding
- Menorrhagia, hematuria, easy bruising, hemarthrosis, and excessive bleeding during or after surgery, childbirth, or trauma.

Coagulation factor XI (PTA) deficiency

Concept

A rare inherited bleeding disorder characterized by a reduced level and/or activity of factor XI, also known as haemophilia C. It is transmitted in an autosomal recessive manner and affects women and men equally.

Etiology

The deficiency is caused by mutations in the F11 gene (4q35) that controls the production of plasmatic factor XI. Unlike what occurs in most coagulation factor deficiencies, the severity of bleeding manifestations is poorly correlated with factor XI levels.

Clinical picture

Most people have few symptoms. The relationship between the amount of FXI in a person's blood has little to do with the severity of their symptoms. The symptoms are very varied, the most common symptoms being

- Abnormal bleeding during or after injury, surgery, or childbirth.
- Epistaxis and menorrhagia in women.
- Bleeding tendency after tooth extraction.

Unlike hemophilia A and B, bleeding into joints and muscles is not common.

Glanzman's disease (Glanzman's thrombasthenia)

Concept

It is an inherited bleeding disorder, characterized by severely reduced or absent platelet aggregation despite stimulation by multiple physiologic agonists. Glanzman's Thromboasthenia (GT) is a rare disorder characterized by clot retraction abnormality, autosomal recessive inheritance with a worldwide distribution that predominates in the Asian region, in areas where consanguineous couples are frequent. Clusters of patients with the disorder have been identified, and founder mutations have been identified in several populations.

There are three types of GT: type 1 in which detectable GP IIb-IIIa is lacking; type 2, in which there is only 10-20% of this normal GP on the platelet surface; and type 3, characterized by presenting receptor dysfunction, with normal GP levels [1,2,13].

Etiology

The platelet αIIb β3 integrin receptor is required for platelet aggregation induced by physiological agonists such as: adenosine diphosphate (ADP), epinephrine, thrombin, collagen, and thromboxane A2 (TXA2). Consequently, abnormalities in this receptor generate a failure in the formation of the platelet plug, in sites of vascular injury and excessive bleeding.

Alterations in either αIIb integrin or β3 integrin result in the same functional defect, because both subunits are necessary for normal receptor function. Subsequent processes: post-translational processing and transport to the platelet membrane, require that the complex be intact; since this protects each of the GP from proteolytic digestion. Thus, if there is an absence or inability of the α IIb or β3 integrin to form this complex with the correct structure, the other subunit is rapidly degraded through a proteosomal mechanism.

Clinical picture

The clinical manifestations are variable, depend on age and sex, and are considered a serious bleeding disorder, since most patients (75%) require transfusion of blood or platelets during their lives. Common symptoms include:

- Mucocutaneous and gastrointestinal bleeding, which can be life-threatening and can be triggered spontaneously or by trauma.
- Presence of hemarthrosis, intracranial hemorrhage and visceral hematoma; however, they are the least frequent.

Based on pediatric age classification, clinical manifestations may vary. In neonates or neonates (first 28 days), purpura may present immediately after birth, but is often not dramatic; in infants and toddlers (28 days to 23 weeks) the first signs are petechiae on the face and subconjunctival hemorrhage associated with crying; children (2 to 11 years of age), on the other hand, tend to present a severe clinical picture of bleeding that includes bruises on the fingertips, bleeding at vaccination sites, and recurrent or severe episodes of epistaxis or gingival bleeding, which are not respond to conventional management. Menorrhagia occurs in adolescent women.

Hemophilia A and B

Concept

Hemophilia A and B are diseases characterized by spontaneous or prolonged bleeding due to deficiencies of factors VIII and IX. Factor VIII (FVIII: C) deficiency is known as hemophilia A, while factor IX (FIX: C) is known as hemophilia B or Christmas disease.

There are similarities between both types of hemophilia; Although clinically they are indistinguishable, the severity of the clinical picture is greater in hemophilia A than in B. The distinction between the two is not only of academic interest, but is also important for their treatment, due to the differences between the molecules of factors VIII and IX. They are synthesized in the same place, the hepatocyte, but have different half-lives (15 hours for factor VIII and 24 hours for IX), and have different stability characteristics (factor VIII is labile, whereas factor IX is stable). in conservation at 4ºC) [1,2,13].

Etiology

Hemophilia A or B has a recessive inheritance linked to the X chromosome (more specifically on the long arm of said chromosome, Xq28 the F8 gene and Xq27 the F9 gene), that is, women carry the disease and men manifest it. This means that the children of a carrier woman have a 50% chance of having the abnormal gene. Approximately 70-75% of hemophiliacs have a family history of the disease, meaning that 25-30% of cases have a de novo mutation.

According to its form of inheritance, it can be concluded that

- All the daughters of a hemophiliac are obligate carriers.
- All children of a hemophiliac are normal.
- Approximately half of the sisters of a hemophiliac are carriers.
- About half of the children of a carrier will be hemophiliacs.
- About half of the daughters of a carrier will be carriers.

On the other hand, the presence of hemophilia in women only occurs in the following cases

- Extreme random lyonization.
- Daughter of a hemophiliac father and carrier mother.
- Association of the disease with Turner syndrome.

Clinical Chart

The clinical data for the two types of hemophilia are substantially identical and vary only in relation to the degree of deficiency. The symptom par excellence of hemophilia is bleeding and the intensity of this will depend on various factors, namely: circulating

level of the deficient factor, presence of inhibitors, trauma, type of daily physical activity and sports, among others. This means that a severely deficient hemophiliac can bleed with minimal trauma, and even with daily strenuous physical activity such as continuous and persistent walking and climbing stairs.

Most of the symptoms of the hemophiliac patient are due to sequelae and complications of the hemorrhagic syndrome. It is not always possible to find the triggering factor for the appearance of bleeding (spontaneous bleeding), but in general it usually obeys minimal causes that in a normal subject can go unnoticed. Hemophilia A and B, because they are primary defects that involve secondary hemostasis, are clinically manifested by deep bleeding, such as:

- Hemarthrosis (intra-articular bleeding)
- Muscle bruises
- Hematuria
- Gastrointestinal bleeding
- Postoperative bleeding
- Mouth bleeds

Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura)

Concept

A condition characterized by immunological platelet destruction. Formerly known as idiopathic thrombocytopenic purpura, immune thrombocytopenia (IT) can cause purple bruises, as well as small reddish and purple dots that look like a rash [1,2,13].

Etiology

IT usually occurs when the immune system mistakenly attacks and destroys platelets. It can be caused by

- Medicines
- Infections, usually viral infections including hepatitis, chicken pox and HIV.
- Pregnancy
- Immune disorders such as rheumatoid arthritis and lupus.
- Low-grade lymphomas and leukemias
- Sometimes IT is idiopathic, meaning the cause is unknown.

Clinical picture

Immune thrombocytopenia may not cause any signs or symptoms. When they do occur, they may include the following

- Platelet count less than 100,000 platelets.
- Tendency to bruise and excessive bruising
- Superficial bleeding on the skin that appears as small reddish-purple spots (petechiae) that look like a rash, usually on the lower legs
- Bleeding from the gums or nose
- Bloody urine, vomit, or stools
- Unusually heavy menstrual flow
- Intracranial hemorrhage

Von Willebrand's disease

Concept

Von Willebrand disease (VW) is transmitted in an autosomal dominant fashion; it is the most common inherited bleeding disorder. It is caused by a decrease in the amount of von Willebrand factor (VWF) or by the presence of a qualitatively abnormal VWF in the circulation. Rarely, VW disease can be an acquired disorder.

It affects both sexes equally, but there are more women diagnosed probably due to excessive bleeding in the female population of reproductive age. It does not show preferences for any specific race or geographic area. Type 1 VW disease, with a mild to moderate decrease from a normal VWF, constitutes 65 to 80% of cases; type 2, which groups those with functionally abnormal VWF, occurs in 20 to 35% of cases, and type 3, with complete absence of VWF, affects around 1 per million inhabitants.

There are three different types: VWD1, VWD2, VWD3. VWD2 in turn is divided into four subtypes, making a total of six types of VW disease. VWD1 and VWD3 present quantitative deficiencies either partial (type 1) or total (type 3) and VWD2A, 2B, 2M and 2N present qualitative deficiencies.

Etiology

The VWF gene is located on the short arm of chromosome 12 and consists of 52 exons. There is a partially replicated pseudogene on chromosome 22, which hinders molecular analysis. Exon 28 encodes essential sites and is the region with the most mutations.

The VWF gene encodes the synthesis of a 2813 amino acid pre-pro-VWF. This protein undergoes significant post-translational modifications. First the removal of the signal peptide, of 22 amino acids, then the dimerization of pro-VWF through disulfide bridges. Dimers are transported from the endoplasmic reticulum to the Golgi apparatus where multimers are formed. The propeptide (VWFpp) is released giving rise to the mature VWF.

Both VWF and VWFpp are released into the plasma in a 1:1 ratio. After multimerization, VWF is stored in the Weibel Palade bodies of endothelial cells and in the alpha granules of platelets, from where it can be released by various stimuli.

Stored, as well as newly released, VWF have extra-large multimeric forms that are highly reactive and bind GpIb. The released VWF is cleaved by a metalloprotease, ADMTS13, in the A2 domain. There are two types of VWF secretion from endothelial cells: 1) constitutive and 2) regulated. When the plasma VWF level increases, factor VIII also increases, but it is not known whether this association occurs inside or outside the endothelial cell.

The VWF has a half-life of 8 to 12 hours and the propeptide 2 to 3 hours. Blood group 0 would favor VWF clearance; Group 0 carriers have 20 to 30% lower VWF levels.

Clinical picture

- Excessive mucocutaneous bleeding, such as epistaxis, easy ecchymoses.
- Bleeding after dental extraction or post surgery [13].
- Menorrhagia in women.

The most important surgical challenges that reveal the bleeding tendency are dental extractions, rhinoplasties, in surgery with local anesthetics, with general anesthesia there are multiple interventions that are considered high risk. Bleeding can be immediate, but sometimes it is delayed, as in fibrinolytic disorders. Hemarthroses are exceptional, except in type 3 VWD.

Bleeding is generally mild to moderate in type 1 VWD and is often more severe in type 2. There is no clear correlation between symptoms and VWF levels.

The most serious cases present

- Bleeding in the urine
- Black or tarry (melena) or bloody stools
- Bleeding in the joints.
- Easy appearance of ecchymosis.
- Stomatological risk in the patient with bleeding disorders

In patients with platelet disorders, it is imperative to work as a team with the hematology specialist for the care of these patients; Before dental intervention, the number of platelets must be above 100,000 platelets per mm3. Substitution therapy in these disorders is platelet concentrate. These hereditary or acquired disorders require joint planning by different multidisciplinary groups. Stomatological procedures represent a challenge, under the condition that the oral cavity is a hemostatic challenge. Continuous uncontrolled bleeding is the main risk, it has serious and serious complications such as the presence of bruises or bleeding that is difficult to control, conditions significant morbidity and mortality by being able to perform a compressive effect on the aerodigestive tract.

It is necessary to take all local measures such as topical thrombin in combination with oxidized cellulose, as well as the use of antifibrinolytics to protect the clot and prevent bleeding, avoid suturing the tissues and prefer local hemostasis with gauze. The diet or food must be soft to avoid gum trauma. The use of aspirin and NSAIDs for pain relief is contraindicated with the exception of acetaminophen because it does not inhibit platelet aggregation.

Good oral hygiene should be indicated, which includes the correct use of the toothbrush, since this is the best prevention to help control plaque bacteria and avoid calculus formation, capable of causing bleeding episodes.

In patients with coagulation factor disorders, hematologists and dentists know that the majority of patients with hemophilia and von Willebrand Disease (VWD) are carriers of multiple and advanced caries for fear of bleeding from toothbrushing.

In the past, dental extraction in patients with VWD and hemophilia required transfusion of blood products and prolonged hospitalization. Replacement therapy with clotting factor concentrates improved this situation, but there was a risk of viral infections and the formation of inhibitors against the transfused factors, currently recombinant products (not derived from plasma) reduce the risk. Treatment with Desmopressin produces the release of Factor VIII and Factor VW in patients with mild hemophilia and VWD type I, being an alternative to the transfusion of coagulation factor concentrates. Other forms of therapy are antifibrinolytic agents and local hemostatic methods, which are necessary but not sufficient in many patients. One goal of dental extraction in patients with bleeding disorders is to prevent bleeding and avoid the use of plasma-derived products.

In hemophiliacs and VWD patients, trunk anesthesia should be avoided if possible due to the danger of deep bleeding, preferring infiltrative, intrapulpal and intraligamentary anesthesia and only performing essential surgery and avoiding elective surgery.

Temporary teeth should not be extracted before their natural fall. No more than two teeth should be extracted per session, removing bone splinters, calculus, which hinder hemostasis. In the postoperative period, antifibrinolytics will be indicated in the form of mouthwash, for three to four minutes, repeating every 6 hours for 5 to 7 days. The gauze moistened with the antifibrinolytic should be placed on the extraction site for 20 minutes [1,2,13].

When the patient suffers from hemorrhage in the postoperative period, he should be reassessed by the treating team, to decide if he should be transfused again with replacement factor and continue oral antifibrinolytic therapy. The use of suture should be avoided; if it were necessary to perform it, non-absorbable suture should be used to prevent the inflammatory response, which has fibrinolytic action.

Scaling and curettage must be performed with prior authorization from the hematologist and with the use of antifibrinolytics in the postoperative period; Endodontics is one of the most indicated treatments for hemophiliac patients.

In dental surgery treatments, it is advisable to isolate the operating field with a rubber dam for several reasons: High-speed sharp instruments can injure tissues, especially in children; in addition, the rubber dam retracts the lips, cheeks, tongue and protects them from any laceration.

The patient who presents abscesses with painful symptoms will receive antibiotic medication and the use of acetaminophen will be recommended. By the time the abscess is drained, the patient should receive replacement therapy, raising factor VIII or IX between 30 to 50%, depending on the deficit.

Replacement of the deficient factor is indicated by the hematologist and will depend on the severity of the disorder. In hemophilia A and VWD, the replacement therapy used is FV III precipitated or concentrated blood, and in hemophilia B fresh or concentrated F IX plasma is used. These results demonstrated that tranexamic acid mouthwash is effective in controlling bleeding in mild and moderate hemophiliac patients undergoing minor dental procedures, reducing the risks of transfusions.

Fibrinolytic activity has been widely demonstrated in the oral cavity, both in saliva and in the gingival fluid of clinically healthy gums, and it has been pointed out that this activity increases in gingival inflammatory processes, contributing to bleeding episodes in patients with blood dyscrasias. In this regard, the studies carried out in hemophiliacs and in patients without hemorrhagic diseases, but with different degrees of periodontal disease, where the fibrinolytic activity of gingival fluid was compared, show that patients with hemophilia have an increase in the fibrinolytic activity of gingival fluid that causes bleeding, but that this increase is not due to the hemorrhagic disease, but rather to the presence of periodontal disease [7-9].

Once the patient comes to the consultation, all the complications that may arise must be taken into account, both to avoid them and to know how to deal with them. Therefore, we must have in consultation the medications indicated to control bleeding in each case, this being the sign that occurs most frequently. Among these drugs we have: Epsilon Amino Caproic, Tranexamic acid, Fibrin foam, Topical Thrombin plugs, vitamin K and K1. These drugs are used: some, at the time of bleeding and others, prior to treatment to prevent it.

White Blood Cell (Leukocyte) Disorders

leukocytes

- Leukocytes (from the Greek λευκός [leukós] 'white', and κύτος [kytos] 'bag', hence they are also called white blood cells) are a heterogeneous group of blood cells that carry out the immune response, thus intervening in the defense of the body against foreign substances or infectious agents (antigens). They originate in the bone marrow and lymphatic tissue. Leukocytes are produced and derived from multipotent cells in the bone marrow, known as hematopoietic stem cells. White blood cells (leukocytes) are the only blood cells found throughout the body, including blood and lymphoid tissue.
- The term "white blood cell" derives from the appearance of a blood sample after it has been centrifuged. Leukocytes are found in the "buff," a thin, typically white layer of nucleated cells that lies between red blood cells and blood plasma. If there are large numbers of neutrophils in the blood sample, the buffy coat may appear green, because they produce a heme-containing enzyme called myeloperoxidase.
- The total count of leukocytes is currently done by automated devices with great precision and accuracy. A value between 4,000 and 11,000 leukocytes/μL is accepted as normal.

Characteristics

- Leukocytes (white blood cells) are mobile cells that are temporarily found in the blood, thus, they form the cellular fraction of the figurative elements of blood. They are the hematic representatives of the white series. Unlike erythrocytes (red blood cells), they do not contain pigments, which is why they are called white blood cells.
- They are cells with nuclei, mitochondria and other cellular organelles. They are able to move freely using pseudopods. Its size ranges from 8 to 20 μm (micrometers). Their life time varies from a few hours. These cells can leave the blood vessels through a mechanism called diapedesis (they prolong their cytoplasmic content), this allows them to move outside the blood vessel and have contact with the tissues inside the human body.

Classification

All leukocytes are nucleated cells, but are otherwise distinct in form and function.

Leukocytes are divided into two major classes

- Granulocytes (neutrophils, eosinophils, and basophils)
- Agranulocytes, which lack specific granules, are mononuclear and have a larger nucleus than granulocytes. They are monocytes and lymphocytes.
- By lineage, white blood cells are divided into: myeloid (composed of granulocytes and monocytes) and lymphoid (T lymphocytes, B lymphocytes, and natural killer cells (NK cells). Neutrophils.

Neutrophils defend the body against viral, bacterial, or fungal infections. They are usually the first to respond to a microbial infection; their activity and death in large numbers form the pus. Neutrophils are commonly referred to as polymorphonuclear leukocytes (PMNs). They have a multilobed nucleus that can resemble multiple nuclei, hence the name polymorphic nuclear leukocyte.

The cytoplasm may appear transparent due to the granules staining pale lilac. Neutrophils are responsible for phagocytosing bacteria and are present in large numbers in pus. These cells are not able to renew their lysosomes (used during the digestion of microbes) and die after having swallowed a few pathogens. Neutrophils are the most common cell type found in the early phases of acute inflammation. They make up 60 to 70% of the total leukocytes in the human blood. The half-life of a circulating neutrophil is approximately 5.4 days.

Eosinophils

Eosinophils, first and foremost, deal with parasitic infections. They are also the predominant inflammatory cells during an allergic reaction. The most important causes of eosinophilia include allergies such as: asthma, allergic rhinitis, and hives; as well as parasitic infections. In general, its nucleus is bilobed. The cytoplasm is filled with granules that, on eosin staining, assume a characteristic orange color.

Basophils

Basophils are mainly responsible for allergic responses, since they release histamine, causing vasodilation. Its nucleus is bi- or trilobed, but it is difficult to detect, as it is hidden by the large number of coarse granules, these granules are characteristically blue under Hematoxylin and Eosin (H&E) staining.

Lymphocytes

Lymphocytes are more common in the lymphatic system than in the bloodstream. They are distinguished by a strongly staining nucleus whose location may or may not be eccentric, and by having little cytoplasm. Lymphocytes include

B cells, which produce antibodies capable of binding, blocking, and promoting the destruction of pathogens, as well as activating complement.

T cells

- **CD4+ helper cells:** these are T cells that express the CD4 co-receptor and are known as CD4+ T lymphocytes. These cells have T cell receptors (TCRs) and CD4+ molecules that together recognize antigenic peptides presented on class-II major histocompatibility complex (MHC) molecules by antigen presenting cells (APCs). Helper T cells produce cytokines and carry out other functions that help coordinate an appropriate immune response. In an HIV infection, the count of these T cells are the main index to identify the integrity of the individual's immune system.
- **CD8+ cytotoxic cells:** these are T cells that express the CD8 co-receptor and are known as CD8+ T lymphocytes. These cells bind to antigens presented on MHC class-I molecules on virus-infected cells or tumor cells. Almost all nucleated cells have MHC class-I.
- **γ δ T cells:** possess an alternative T cell receptor (different from the αβ T cell receptor found on conventional CD4 and CD8 T cells). They are more commonly found in tissues than in blood. γδ T cells share characteristics with helper cells, cytotoxic cells, and natural killer cells.
- **Natural Killer cells:** these are cells capable of killing body cells that do not have MHC class-I molecules, or that have stress markers such as MIC-A (MHC class I polypeptide-related sequence A). Downregulation of MHC class-I expression and upregulation of MIC-A can occur when cells of the organism are infected by a virus or are cancerous.

Monocytes

Monocytes share the "vacuum cleaner" function (phagocytosis) with neutrophils, but they are more long-lived and also have an extra function: presenting parts of pathogens to T lymphocytes so that they can be recognized again and eliminated. Monocytes leave the bloodstream (diapedesis) to become tissue macrophages, which are responsible for removing remains of dead cells and attacking microorganisms. Unlike neutrophils, monocytes are capable of replacing their lysosomal content and their active life is believed to be much longer. Its nucleus is kidney-shaped and does not have granules and contains abundant cytoplasm. Once monocytes leave the bloodstream and enter some body tissue, they go through changes that allow them to phagocytosis (differentiate) and become macrophages.

Fixed leukocytes

Some leukocytes migrate to body tissues to reside there permanently and not in the bloodstream. Often these cells have specific names depending on what tissue they take up residence in; an example is the fixed liver macrophages, known as Kupffer cells. These cells continue to play an important role in the immune system.

Histiocytes

- Dendritic cells (although these usually migrate to local lymph nodes when ingesting antigens)
- Mast cells
- Microglia

Disorders

There are two main categories of disorders that involve white blood cells: proliferative disorders and leukopenias. In proliferative disorders there is an increase in the number of leukocytes; this increase is commonly reactive (for example, when due to infection), but it can be cancerous, too. In leukopenias there is a decrease in the number of leukocytes. Both disorders are quantitative. It has been observed that the apoptotic processes in leukocytes could be related to the generation of free radicals in the mitochondria from a change in intracellular calcium homeostasis. Qualitative disorders of white blood cells fall into a different category; in these the number of leukocytes is normal, but the cells do not function properly.

Leukopenias

- Decrease in the number of white blood cells (leukocytes) to less than 4000 cells per microliter of blood (4x109 per liter), making those affected more susceptible to infections.
- A range of disorders can cause a decrease in white blood cells. The decreased cell type is usually the neutrophil. In this case, the decrease may be called neutropenia or granulocytopenia. In rarer cases, a reduction in the number of lymphocytes (called lymphocytopenia or lymphopenia) may be found.

Neutropenia (Agranulocytosis, Granulocytopenia)

Concept

- Neutropenia is a decrease in the normal number of neutrophils in the blood, below 1,500 neutrophils/ml or 1.5 x 109/L.
- Neutropenia can be acquired or intrinsic. A decrease in neutrophil levels in a laboratory test may be due to decreased production or increased clearance of the same cells from the bloodstream [1,2,13].

Etiology

Medications: chemotherapy, sulfa or other antibiotics, phenothiazides, benzodiazepines, antithyroids, anticonvulsants, quinines, quinidines, indomethacins, procainamide, thiazides.

Radiation.

- **Toxins:** alcohol, benzenes.
- **Intrinsic disorders:** Fanconi syndrome, Kostmann syndrome, cyclic neutropenia, Chediak-Higashi.
- **Immunodeficiency:** collagen disorders, AIDS, rheumatoid arthritis.
- **Dysfunction of blood cells:** megaloblastic anemia, myelodysplasia, marrow failure, marrow replacement, acute leukemia.
- Serious infections.
- Miscellaneous: starvation, hypersplenism.

Clinical picture

The symptoms of neutropenia are associated with the underlying cause of the decreased neutrophils. They do not usually present specific symptoms; hence, in many cases they are not diagnosed until an infection appears. Some warning signs are

- Recurrent infections with or without fever (pneumonia, pyelonephritis, sepsis, repeated colds).
- Appearance of abscesses, boils, cellulitis, otitis among others that do not respond to the usual antibiotics and that are recurrent.
- When it is caused by drugs, those affected may have fever, rash and swollen lymph nodes.

Lymphocytopenia (Lymphopenia)

Concept

It is defined as a total lymphocyte count less than 1.0x109/L, the most commonly affected cells are CD4+ T cells. As in neutropenia, lymphocytopenia can be of acquired or intrinsic origin and there can be several causes.

Etiology

- Inherited immunodeficiency
- Severe combined immunodeficiency
- Common variable immunodeficiency
- Ataxia-telangiectasia
- Wiskott-Aldrich syndrome
- Immunodeficiency with short-limbed dwarfism
- Immunodeficiency associated with thymoma
- Deficiency in purine nucleoside phosphorylase
- Genetic polymorphism.
- Bone marrow dysfunction
- Aplastic anemia.

Infectious diseases: viral (AIDS, SARS, Nile encephalitis, hepatitis, herpes, others), bacterial (tuberculosis, typhoid fever, pneumonia, rickettsiosis, sepsis), parasitic (acute phase of malaria).

- **Medications:** chemotherapy.
- Radiation.
- Major surgeries.
- **Miscellaneous:** extracorporeal membrane oxygenation (ECMO), kidney or bone marrow transplantation, hemodialysis, renal failure, severe burns, celiac disease, severe acute pancreatitis, enteropathy, vigorous exercise, carcinoma.
- **Immunopathology:** Arthritis, systemic lupus erythematosus, Sjögren's syndrome, myasthenia gravis, systemic vasculitis, dermatomyositis, Wegener's granulomatosis.
- **Nutrition/diet:** Alcohol abuse, zinc deficiency.

Pancytopenia

Concept

The term pancytopenia refers to a decrease in the three formed elements of the blood: erythrocytes, leukocytes, and platelets. It is not a specific entity, but rather a triad of findings that occurs due to various pathological processes that range from mild infections to potentially lethal conditions, such as bone marrow aplasia and some neoplasms, which makes it necessary to rule out these serious pathologies as soon as possible. It is a frequent hematological problem in clinical practice and should be suspected when a patient presents with pallor, fever and a tendency to bleed [1,2,10,12].

Etiology

- A study of 132 adults with pancytopenia (with no history of hematologic malignancies, OM study, or cytotoxic chemotherapy), to determine etiology and identify its relationship to clinical and laboratory findings, revealed the following results:
- Clonal hematopoietic disorders: myeloid neoplasms such as acute myeloid leukemia, myelodysplastic syndrome, as well as lymphoid neoplasms: non-Hodgkin lymphoma, hairy cell leukemia, and B-cell acute lymphoblastic leukemia.
- Nonclonal hematopoietic disorders: aplastic anemia, megaloblastic anemia, and human immunodeficiency virus infection.
- Clonal hematopoietic disorders were associated with a higher incidence of cytopenias and leukoerythroblastic imaging than nonclonal disorders. Almost two thirds of the patients with de novo pancytopenia had a clonal etiology, myeloid neoplasms being the most common, and where hematic cytometry and peripheral blood smear findings pointed to a clonal etiology.

Clinical picture

- The initial clinical picture of patients with pancytopenia is variable; the onset is often insidious and its manifestations depend on the severity of the anemia, leukopenia, or thrombocytopenia.
- Anemia can present with symptoms of weakness, fatigue, exercise intolerance, dyspnea and in geriatric patients with angina pectoris.
- Leukopenia, mainly neutropenia, presents an increased susceptibility to bacterial infections, especially in the oral cavity, anorectal mucosa, urinary tract, and respiratory tract.
- Thrombocytopenia can manifest semiologically as a purpuric syndrome and is serious when there is CNS bleeding.
- The other clinical and laboratory findings reflect the underlying disease and generally serve to quickly determine the differential diagnosis.

Proliferative disorders

An increase in the number of white blood cells in the blood circulation is known as leukocytosis. This increase is commonly caused by inflammation. There are four main causes: cell overproduction in the bone marrow, increased release of cells stored in the bone marrow, decreased ability to adhere to the wall of blood vessels, decreased uptake by tissues. Leukocytosis can affect one or several cell lines and can be neutrophilic, eosinophilic, basophilic, monocytosis, or lymphocytes.

Neutrophilia

Concept

Neutrophilia is an increase in the total neutrophil count in the peripheral circulation greater than 7.5x109/L. Normal values vary according to age. Neutrophilia can be caused by a direct disease of the blood cells (primary disease). It can also occur as a consequence of an underlying (secondary) pathology. Most cases of neutrophilia are secondary to inflammation.

Etiology

Conditions with functional neutrophils - hereditary neutrophilia, chronic idiopathic neutrophilia.
Pelger-Huet anomaly.

- Down's Syndrome.
- Leukocyte adhesion deficiency.
- Familial urticaria.
- Leukemia.
- secondary causes
- Infections.

Chronic inflammation: especially juvenile rheumatoid arthritis, rheumatoid arthritis, Still's disease, Crohn's disease, ulcerative colitis, granulomatous infections (such as tuberculosis), and chronic hepatitis.

- Smoking.
- Stress: exercise, post-surgery.
- Drug-induced: corticosteroids.
- Cancer: by growth factors secreted by the tumor or by invasion of the bone marrow.

Increased destruction in the peripheral circulation can stimulate the bone marrow. This can occur in hemolytic anemia and idiopathic thrombocytopenic purpura.

Lymphocytosis

Concept

Lymphocytosis is an elevated lymphocyte count above 3000 lymphocytes in one microliter of blood (30 x 109/L).

Etiology

It can have a high count and no symptoms, but it usually appears after an illness. Among the causes we find

- Infection (bacterial or other)
- Blood or lymphatic system neoplasia.
- An autoimmune disorder.
- Specific causes include:
- Acute lymphocytic leukemia
- Chronic lymphocytic leukemia

- Cytomegalovirus infection.
- Hepatitis A, B and C
- HIV AIDS
- Hypothyroidism
- Lymphoma
- Mononucleosis
- Other viral infections
- clinical picture

Some symptoms are

- Weakness
- Fatigue
- Weightloss
- Shaking chills
- Fever
- Night sweats
- Swollen lymph nodes
- leukocyte deviation

In hematology, a white series deviation, leukocyte deviation, leukocyte deviation, or leukocyte formula deviation is a change in the differential count or leukocyte formula, with changes in the ratios between the different stages of development of granulocytes to neutrophils, a subgroup of white blood cells (leukocytes). It can consist of the appearance of immature neutrophil granulocytes, which is known as "shift to the left" or the appearance of more mature neutrophils called "shift to the right").

In case of infection and/or inflammation, the organism reacts with an increase in the total number of total leukocytes (leukocytosis) as well as in the number of neutrophils (neutrophilia). In the first six to eleven hours, this occurs due to a greater release of these cells from the bone marrow, the site of leukocyte production. After two to three days, increased neutrophil formation appears in the bone marrow.

Reactive shift to the left is the increase in immature forms of neutrophils. In addition to functionally mature neutrophils (so-called segmented neutrophils), their precursors appear, such as rods or band cells, metamyelocytes, myelocytes, and even promyelocytes, in a percentage equal to or greater than 3-5%. This occurs by the precipitous release of these immature cells due to their high expenditure on infection or inflammation [1,2,13].

This reactive leftward shift in the blood count is found, for example, in most bacterial infections, and is often accompanied by the presence of toxic granulation and/or Döhle bodies. It also occurs in myeloproliferative syndromes and invasive diseases of the bone marrow.

There are two forms of reactive left shifting

- In the regenerative shift to the left, the number of bands or bands (immature forms) increases, and the total number of neutrophils also increases.
- In degenerative left shift, the number of immature cells is increased, but the total number of neutrophils is reduced (neutropenia) or normal.

A shift to the left without neutrophilia (degenerative) indicates a greater consumption of these cells, due to the inability of the bone marrow to replace the spent ones. In this case, the evolution is usually controlled with new analyses, assessing the evolution of the deviation to the left and the relative and absolute neutrophil count.

A pathologic shift to the left refers to a shift to the left that can go as far as the appearance of myeloblasts, which represent the less mature form of granulopoiesis. Pathologic shift to the left occurs mainly in primary blood diseases (leukemia) and in the acute phase is often associated with leukocytosis or even hyperleukocytosis. In some infectious conditions, especially pneumonia, blasts may appear temporarily, disappearing after the causative infection has healed.

By "shift to the right" is meant the increase in aged neutrophils, so-called hypersegmented neutrophils. This may be due to decreased migration of neutrophils from blood vessels, for example, by increased endogenous production of

- Glucocorticoids, by the administration of glucocorticoids as anti-inflammatories, or in anemia due to vitamin B12 and/or folic acid deficiency (eg, pernicious anemia).
- Stomatological risk in patients with proliferative leukocyte disorders
- Leukocyte abnormalities comprise a group of diseases that affect the number, shape, or function of white blood cells, predisposing patients to bacterial and fungal infections.
- Leukocytes are defense cells against microorganisms, and are involved in the demolition of old, non-functional or necrotic cells and tissues. According to their morphological and functional characteristics they are divided into: granulocytes (neutrophils, eosinophils, basophils), and agranulocytes (lymphocytes and monocytes). The main function of neutrophils is to defend the body from infectious agents through phagocytosis and enzymatic destruction.

Eosinophils and basophils are involved in allergic-inflammatory reactions. T lymphocytes in delayed or cellular immune reactions, B lymphocytes in the immediate or humoral immune system. Monocytes act as phagocytes, and are mediators in the immune and inflammatory response through substances such as cytokines and growth factors.

The importance of neutropenia is given by the relationship between the absolute number of neutrophils and the propensity for infections, but it also depends on other factors such as: the mechanism of neutropenia, its duration, the association with other defense alterations, the integrity of the mucocutaneous barriers and the general state of the patient.

Management and treatment of neutropenia

The clinical management of neutropenic states depends on the degree and cause of neutropenia and associated diseases. The main problem is the management of infectious complications. Patients with severe neutropenia are prone to serious pyogenic infections. Preventive measures are essential to limit the number and intensity of infections, as well as the early identification and treatment of existing ones. All these patients must take special dental care to avoid infections and tooth loss.

Stomatological management of leukopenia

- Review BH and with neutrophils <200 or zero only palliative treatment.
- Antibiotic prophylaxis in mild neutropenia, dental procedures of any kind can be performed.
- In moderate or severe neutropenia, oral treatment is contraindicated; In those emergency procedures or those that improve the patient's oral condition, prophylactic antibiotics will be prescribed after consultation with the hematologist.
- Conventional treatment in periods in which neutrophil numbers are within normal parameters.
- Strict control of dental plaque and dental calculus.
- Preventive dentistry.
- Elimination and control of infectious foci.
- Radical treatment in cases that so warrant.
- In the event of leukocytosis it is very important to determine what type of leukocytes is increased, looking at the absolute value and not the percentage, so we will see if it is neutrophilia, lymphocytosis, eosinophilia or monocytosis, rule out associated alterations, a clinical history Thorough examination will guide the diagnosis, thus reducing the risk of complications by determining the cause of leukicytosis.

In persistent leukocytosis with no apparent cause with or without involvement of other series (erythrocytes, platelets) or the presence of adenopathies, and splenomegaly, referral to the hematology service should be made to rule out myeloproliferative or lymphoproliferative processes. We will take into account that the patient already has a condition and that by performing an invasive treatment we can worsen the condition or add another health problem to the existing one.

Odontogenic infections can be the cause of leukocytosis and in this case the stomatological procedure would achieve a decrease in blood leukocytes, since the cause would be eliminated.

Stomatological management

- In leukocytosis of non-odontogenic origin, postpone treatment until the infectious process is resolved.
- In the event that a dental infection is causing leukocytosis, the affected tooth and/or drainage of the abscess, if any, and antibiotic therapy will be canalized, followed by root canal treatment of the affected tooth, curettage or extraction.

Neoplastic disorders of blood cells

Hematologic malignancies are a heterogeneous group of malignancies that affect the blood, bone marrow, and lymph nodes, and because all three systems are linked by the immune system, a hematologic malignancy involving one will affect the other two. The most frequent causes of these disorders are chromosomal translocations, something not often seen in association with solid tumors. This leads to an exclusive approach in the diagnosis and treatment of hematological malignancies.

Acute leukemia

Concept

- Acute leukemia is a disease characterized by the neoplastic proliferation of any cell of the hematopoietic tissue. It is a very serious disease that can cause death in a short period of time, if not treated properly.
- Leukemia is classified according to the cell from which the disease originates. This cell is usually called a blast; Two large families of acute leukemia are recognized: lymphoblastic (ALL) and myeloblastic (AML), a very useful classification, since acute leukemia is a condition with variable behavior depending on the type of cell affected.
- It is the most common neoplasia in children under 15 years of age, a group in which it constitutes 30% of all cancers. The condition predominantly affects the male gender; the lymphoblastic variety predominates in males.
- Acute lymphoblastic leukemia presents at least three defined morphological variants: L-1, L-2, and L-3; the difference between one group and another is based on the size, the degree of maturation of the nucleus, the presence of nucleoli and vacuoles.

Etiology

- The exact cause of acute leukemia is unknown. There is a familial tendency, since the siblings of a patient with leukemia, especially if they are identical twins, have a higher risk of being affected than those who do not have relatives with this problem. In some cases, exposure to mutagens, such as radiation, or chemicals such as benzene derivatives is clearly corroborated.
- It is also possible that some drugs such as chloramphenicol, or alkylating antineoplastics, such as cyclophosphamide, can cause changes that lead to the appearance of leukemia. On

the other hand, acute leukemia is more common in individuals with trisomy 21 and other inherited disorders, as it is in individuals with congenital or acquired immunodeficiencies. Viruses are currently highly suspected of causing disease in predisposed organisms and there are different models or examples in animals that support this theory. For sure, the cause of leukemia is multifactorial and does not depend on a single abnormality.

Clinical Chart

- The most common symptom of ALL is fatigue or weakness (92%)
- Bone or joint pain (80%) and fever (70%)
- Weight loss (66%) and abnormal masses (62%)
- purpura hemorrhage
- Infection
- The most common signs are splenomegaly, adenomegaly, hepatomegaly, and pain on sternal pressure.
- Paleness and young children (infants) show irritability.
- All the clinical data are explained by the decrease in hemoglobin and hematocrit, and by the accompanying thrombocytopenia and neutropenia, in addition to the increase in the percentage of blasts in the bone marrow, blood, spleen, liver, and lymph nodes.
- Children younger than 2 years of age may present with massive enlargement of the spleen and liver, hyperleukocytosis, chromosome 11q23 abnormality, presence of lymphoblasts in the cerebrospinal fluid (CSF), and slow response to chemotherapy.

Chronic lymphocytic leukemia

Concept

- Chronic lymphocytic leukemia (CLL) is a disease characterized by the proliferation and accumulation of mature-appearing lymphocytes in the bone marrow, blood, lymph nodes, and spleen.
- This is the most common leukemia in adults in Western countries, the incidence depends on age; it is rare before the age of 40 and increases progressively until reaching 50 cases per 100,000 people over 70 years of age. It occurs predominantly in the male gender, with a male-female ratio of two to one. There seems to be a hereditary factor that leads to the aggregation of cases in the so-called familial LLC. It occurs more frequently in the Caucasian population than in the black race.

Etiology

- The cause of CLL is unknown, but it has been shown that farmers, workers who are in contact with asbestos and other types of jobs with toxics have a higher risk of developing this disease; this suggests that occupational exposure may play a role in the cause. This condition is the only leukemia that has not been linked to exposure to radiation and alkylating agents. Numerous attempts have been made to assess the causative role of DNA and RNA viruses in CLL, without finding direct evidence of viral infection as the cause of CLL.
- In CLL, the malignant cells are of lineage B with a degree of maturation intermediate between pre-B and mature B lymphocytes, which have a morphological appearance very similar to that of normal mature cells; less than 10% may be prolymphocytes. Malignant lymphocytes are generally resistant to programmed cell death or apoptosis, so their survival in the circulation is very long. This is the presence of the mutation in the variable region of the heavy chain of the affected immunoglobulin, which is related to the pathogenesis of the disease.
- The most frequent chromosomal abnormalities are aneuploidies and deletions, while translocations are rare. The most common isolated abnormality is the 13q14 deletion, which occurs in 55% of patients.

Clinical picture

Patients with CLL can present with a wide spectrum of signs and symptoms. Currently, more than half of cases are discovered as an incidental finding on a complete blood count showing leukocytosis with lymphocytosis in asymptomatic individuals. In other patients, the diagnosis is made by studying manifestations such as

- Asthenia and adenopathies
- Increased susceptibility to bacterial (pneumonia) or viral infections, including herpes simplex or zoster.
- Mucocutaneous hemorrhage.
- Local or generalized lymphadenopathy
- Hepatomegaly and splenomegaly, resulting from progressive infiltration by lymphocytes.
- CLL usually presents with cervical lymphadenopathy; however, as the disease progresses, the adenopathy becomes generalized. Splenomegaly can be found in 20 to 30% of cases. Occasionally, it is possible to find infiltration to non-lymphoid organs, such as the prostate, kidney and pleura.

Chronic granulocytic leukemia

Concept

Chronic granulocytic leukemia (CGL) is a clonal myeloproliferative disease with a genetic defect known as the Philadelphia chromosome (CrPh) of the pluripotent stem cell that affects erythroid and megakaryocytic myeloid cells; clonality has been demonstrated in cytogenetic, molecular, and glucose-6-phosphate dehydrogenase studies in 90% of cases.

Etiology

The condition is characterized by a cytogenetic abnormality known as the Philadelphia chromosome associated with the BCR-ABL fusion gene, a reflection of the exchange of genetic material between chromosomes 9 and 22, which is found in the pluripotent stem cell and generates an oncoprotein, p210. BCR-ABL with tyrosine kinase activity, which is generally considered the initiator of the chronic phase of the disease. Biological characteristics of BCR-ABL positive cells are increased proliferation, reduced apoptosis, and impaired adherence to the extracellular matrix.

In relation to the origin of the disease, there are no known environmental or genetic factors that increase the risk of suffering from the disease.

Clinical picture

In 85% of patients the disease is diagnosed in a chronic phase. The initial symptoms are non-specific such as

- Asthenia
- Hyporexia
- Weightloss
- Fever and nocturnal diaphoresis.

There may be manifestations related to splenomegaly, such as left upper quadrant pain, postprandial fullness, or both. There are other less frequent manifestations, such as:

- Bone pain
- Hemorrhage
- Drop
- Nephrolithiasis.

Currently, 40% of cases are asymptomatic at the time of diagnosis. On physical examination, the most common finding is splenomegaly, which is observed in 80 to 90% of cases, and moderate hepatomegaly is detected in one third of patients.

Vera polycythemia

Concept

Like other myeloproliferative syndromes, polycythemia vera (PV), or polycythemia rubra vera, is the result of abnormal proliferation of a pluripotent stem cell that gives rise to clonal hematopoiesis of red blood cells, white blood cells, and platelets, among which erythroid hyperplasia predominates.

Etiology

In vitro cultures of hematopoietic progenitor cells from patients with PV have shown both hypersensitivity of these erythroid progenitor cells to the action of erythropoietin and the ability to form colonies independent of erythropoietin stimulation.

Clinical picture

Patients suffering from PV present symptoms secondary to the increase in blood volume

- Headache
- Asthenia
- Dizziness
- Visual disturbances
- Dyspnea, pruritus, diaphoresis, weight loss; they also have epigastric pain.

A common complication resulting from increased gastric secretion due to high histamine levels caused by existing basophilia. Erythromelalgia (burning pain in the feet and hands, accompanied by erythema, pallor, or cyanosis) is commonly seen and is thought to be secondary to microvascular thrombotic complications. Itching on the skin, particularly after bathing, can be very serious. Patients usually develop gout and the characteristic clinical picture due to the increase in uric acid levels caused by accelerated cell turnover.

- Patients are often thin, which is a reflection of the hypermetabolic state associated with increased hematopoiesis.
- During the physical examination, a plethoric appearance, conjunctival injection, and cyanosis of the skin and mucous membranes can be found; 66% of patients present splenomegaly and arterial hypertension; half also have hepatomegaly.
- Manifestations due to hemostasis disorders are common. Thrombotic complications are the main cause of morbidity and mortality: 66% of them are arterial. Bleeding complications occur in 30 to 40% of patients and are a consequence of functional platelet disorders.

Essential Thrombocytosis (Essential Thrombocythemia)

Concept

Myeloproliferative disorder of clonal origin of stem cells, which has phenotypic expression, primarily in the megakaryocyte and platelet lineage, but affects all blood cells.

Etiology

The cause of essential thrombocytosis (ET) is unknown; however, its clonal origin has been demonstrated. It has an incidence of two cases/100,000 inhabitants/year. This disease usually occurs in people between 50 and 70 years of age, and affects women and men in equal proportions. In this disorder, platelets present various morphological, biochemical, and functional abnormalities, since there is a decrease or absence of cytoplasmic granules along with alterations in platelet size and volume. Platelet aggregometry shows a reduction or lack of response to the usual platelet agonists, such as ADP, thrombin, and collagen.

Clinical picture

- In many cases, the diagnosis is a fortuitous finding during a complete blood count; however, the most common in patients who report symptoms are:
- Hemorrhagic manifestations (especially in the digestive tract and nasal mucosa) or thrombotic manifestations (in most cases, arterial thrombosis).
- These thrombotic manifestations can lead to clinical signs of transient ischemic attack or even stroke, coronary ischemia, intermittent claudication, and erythromelalgia (redness and intense pain, manifested as burning and pain in the extremities, especially the soles of the feet).
- When it occurs in women of reproductive age it can cause:
- Recurrent miscarriages and fetal growth retardation.
- The most common finding on physical examination is grade I splenomegaly (up to 40% of individuals)
- Ecchymosis and other hemorrhagic manifestations that occur more frequently than thrombotic ones.

Hodgkin lymphoma

Concept

This lymphoma is a malignant, lymphoproliferative disease that originates in the B lymphocytes of the lymph nodes, described by Thomas Hodgkin in 1832. Although the origin of the neoplastic cell that characterizes it (Reed-Sternberg cell) is not fully defined, since it shows an inconstant expression of specific antigens for a determined cell lineage, it has lymphoid characteristics; in fact, the classic disease is a monoclonal disorder of the germinal center B lymphocyte.

Rye's (1966) classification, based on that of Lukes and Butler, divides the disease into four histological varieties

- Lymphocytic predominance, 10 to 15%.
- Mixed cellularity, 30 to 50%.
- Nodular sclerosis, 20 to 40%.
- Lymphocyte depletion, 5 to 15%.

Etiology

- The exact cause of this disease is unknown. However, a viral infectious origin has been suggested in people predisposed by genetic factors. Likewise, its development has been related to virus infections, such as Epstein Barr, cytomegalovirus, herpes simplex type 2, and retrovirus.
- A history of infectious mononucleosis, high titers of antibodies to Epstein Barr virus, or both, confers a three-fold increased risk of developing Hodgkin's disease. Deficiency in natural immunity and malnutrition are factors that are considered predisposing. In conclusion, it is possible that the origin of the disease is explained by genetic predisposition and one or more of the factors mentioned.

Clinical picture

Lymphomas are usually asymptomatic diseases. Lymph node enlargement is the most common clinical manifestation

- It is slow, can take months to become apparent, and occurs most frequently in the left supraclavicular fossa.
- Less than 5% of cases present with extranodal invasion.
- The typical patient presents adenomegaly in the cervical or supraclavicular region (75%); the lymph nodes are painless and "elastic" or "rubbery" and slow-growing.
- There is also adenomegaly in the armpits and in the inguinal region (15 and 10% of cases, respectively).

When, in addition to adenomegaly, the patient presents symptoms, it is assumed that he is a carrier of an advanced stage or a more active variety of the disease. Those symptoms can be:

- Fever
- Diaphoresis
- Loss of 10% of body weight in less than six months
- Itching.

These symptoms are observed in the least part of cases. One in five or six patients presents a peculiar pain in the affected lymph nodes after alcohol ingestion, without knowing the cause, but it is related to eosinophilia in the peripheral blood. The fever can be intermittent (Pel-Ebstein type) or daily and predominantly in the evening. It subsides easily with prostaglandin blockers or antagonists, such as indomethacin or naproxen.

As the disease progresses, the patient may present with dysphagia, dyspnea, cough, or chest pain, depending on the location of the tumor [1,2,12,13].

Non-Hodgkin lymphomas

Concept

This neoplastic disease, also known as "unicellular lymphoma" or "malignant lymphoma", originates from abnormal lymphocytes located in the lymph nodes or extranodal lymphoid tissue. (Figure 1 and 2).

Non-Hodgkin lymphomas have a 50% higher incidence in men than in women (Figure 2).

They tend to affect any age group, especially after three years; however, the older the age, the higher the incidence. The average

Figure 1: Female patient with a diagnosis of Non-Hodgkin Lymphoma, front view. Courtesy of Dr. Carlos Juan Puig González.

Figure 2: Female patient diagnosed with Non-Hodgkin Lymphoma, lateral view. Courtesy of Dr. Carlos Juan Puig González.

age of presentation is 45 to 55 years, with a median of 60 to 65 years. In childhood they constitute 10% of all cancers, only below acute leukemia and brain tumors.

The clinical features that affect the behavior of lymphomas can be summarized as follows

- Low grade of malignancy
- Indolent clinical course
- Prolonged survival
- Not curable with chemotherapy
- High degree of malignancy (See image)
- Active clinical course
- Short survival
- Curable with chemotherapy

Etiology

The exact origin of this condition is not precisely known, but infections by viruses and bacteria (Epstein-Barr virus, Helicobacter pylori, etc.), natural or acquired immunosuppression, family history of lymphoma, malignant diseases are considered predisposing factors. autoimmune diseases, exposure to some chemical agents and radiation, some nutritional factors, as well as having received blood transfusions.

Clinical picture

The majority of patients (60 to 80%) come to the clinic for asymptomatic lymphadenopathy. Adenomegaly is very similar to that of Hodgkin lymphoma: it is located more frequently in the neck, armpits, or inguinal region.

- No pain, firm and rubbery consistency nodes.
- Patients with advanced disease may present with B symptoms:
- Unexplained fever greater than 38°C
- Night sweats
- Loss of body weight greater than 10%.

Hepatosplenomegaly is common at this stage. Active lymphomas more frequently invade extranodal sites, such as the skin or the central nervous system (CNS). Primary lymphoma of the brain can be seen in patients with AIDS, with widely varying neurologic findings including increased intracranial pressure, seizures and facial nerve palsies, cognitive and personality changes, or both, which may mimic a psychiatric disorder.

The clinical picture varies according to the type of lymphoma, since the higher the degree of malignancy, the faster the onset of symptoms.

Figure 3: Male patient diagnosed with nasal T/NK cell lymphoma, front view. Courtesy of Dr. Carlos Juan Puig González.

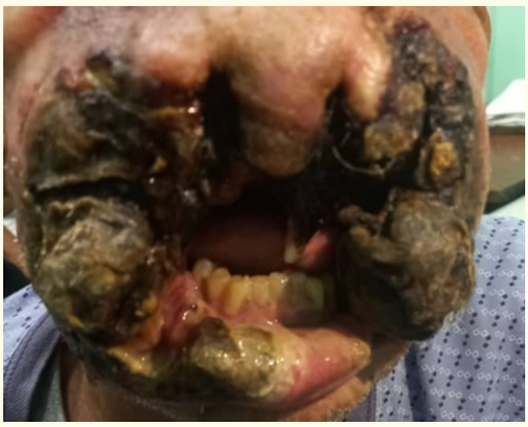

Figure 4: Male patient diagnosed with nasal T/NK cell lymphoma, front view. Courtesy of Dr. Anibal Lázaro Serrú Estevez.

Extranodal lymphoma can be seen at the time of diagnosis or during the course of the disease; the most frequently affected sites are the CNS, eye, sinuses, skin, lungs, gastrointestinal tract, testis, liver, spleen, bone, bone marrow, genitourinary tract, ovaries, and mammary gland.

Multiple myeloma

Concept

Multiple myeloma (MM) is a neoplasm of plasma cells, which replaces normal cells in the bone marrow, causing bone destruction and formation of an abnormal protein called component or M protein.

Etiology

It usually evolves from a premalignant state called monoclonal gammapathy of undetermined significance (MGUS). MGUS is present in 3% of the general population older than 50 years, progressing to MM or a related malignancy at a rate of 1% per year.

Clinical picture

- Most patients present at the time of diagnosis with normochromic normocytic anemia, the causes of which are multiple: bone marrow infiltration by myeloma cells, IL-6-mediated suppression of erythropoiesis, relative erythropoietin deficiency, renal failure, side effects of chemotherapy or radiation therapy, hemodilution, decreased red blood cell half-life, and secondary myelodysplasia.
- Bone pain occurs in 90% of patients and is caused by the infiltration of malignant cells into the bone, but above all by the production of osteoclast activating factors (IL-6, IL-1, tumor necrosis factor, hepatocyte growth factor, and parathyroid hormone-related peptide) by myeloma cells, which destroy bone mass and produce the characteristic lytic lesions of this disease.
- Bone pain initially predominates in the lumbar region and can be confused with symptoms of degenerative joint disease, also common at this age.
- Abnormal or pathological fractures, especially in long bones and vertebrae.
- Hypercalcemia (in 30 to 40% of patients at the time of diagnosis).

Risk of infections due to causes such as: neutropenia, caused by the chemotherapy applied or by fibrosis of the bone marrow, which occurs in 10 to 15% of patients, or by immunosuppression due to altered function of B cells, function altered T cell count (there is suppression of natural killer cell and T cell activity) or chemotherapy or radiation therapy.

- Infection of the respiratory tract, blood, urinary tract, skin and other sites; in 6% of cases it is difficult to define a fever origin.
- Myeloma cells can form tumors in or outside the bone (plasmacytomas) that can cause spinal cord compression, but can occur in the facial region (Figure 5).
- Very high levels of M protein (IgG or IgA) cause hyperviscosity syndrome.
- Renal insufficiency.
- Serum creatinine greater than 2 mg/dl at the time of diagnosis.
- Some patients present with signs of peripheral neuropathy, which can be the result of several factors
    - Direct action of the M protein
    - Neuropathy due to amyloidosis
    - Diffuse infiltration by MM cells in peripheral nerves.
    - Related metabolic diseases
- Bleeding as a result of: thrombocytopenia (in turn due to bone marrow infiltration, immune-mediated, myelodysplasia or effects of chemotherapy), abnormal platelet function, vascular defect due to amyloidosis, acquired VW disease, polymerization abnormalities fibrinogen, circulating anticoagulants, coagulation factor deficiency or accelerated fibrinolysis.
- Among patients with MM, 10-15% have myeloma-related amyloidosis.
- Stomatological risk in patients with Hematological Neoplastics
- Given the variety and complexity of blood cancers, the main risks are bleeding and infection. The dental treatment of these patients must be designed anticipating the occurrence of these complications.

Figure 5: Male patient with solitary bone plasmacytoma. Courtesy of Dr. Carlos Juan Puig González.

Recommendations in dental treatment

It is recommended that the examination, general and oral treatment be integrated into the pre-treatment protocols for cancer. Oral care should be presented in agreement with the oncologist and tailored to the needs.

The intervention must be adapted to the following hematological recommendations

- Elective dental treatments will be carried out only if the number of neutrophils is > 1,000/mm3 and that of platelets > 100,000/mm3.
- Emergency dental procedures to eliminate sources of infection can be carried out in any hematological state, in coordination with the Oncology Service. Platelet replacement is considered if it is < 100,000/mm3.
- Preventive dental procedures (daily): • Neutrophil count > 500/mm3 and platelet count > 20,000/mm3: brush and floss.
- Neutrophil count < 500/mm3 and platelet count < 20,000/mm3: use gauze.
- Antibiotic prophylaxis: should be recommended for patients at risk recommended by the American Heart Association if the number of neutrophils is <500/mm3 and/or the total white cell count is <2000/mm3, the patient has a catheter inserted central venous vein or taking immunosuppressive drugs, under hospital admission.
- The care of patients with leukemia can be divided into three phases of care: pretreatment, during treatment, and post-chemotherapy, bone marrow transplant, and/or radiation.
- Treatment should be carried out only after prior consultation with the oncologist and review of the haematological figures, and after considering the need for antibiotic prophylaxis, it should include usual hygiene procedures and the application of fluoride gel, conservative treatment of soft tissue lesions to maintain them. asymptomatic, restore decayed teeth and replace provisional restorations, establish the necessary pulp treatment. Pulpotomy and pulpectomy can be performed and are preferable to extractions if there is no periradicular involvement. However, teeth with acute or chronic infection and involvement of the periradicular tissues or doubtful prognosis should be extracted.
- From the start of treatment 30 to 45 days after induction of remission by chemotherapy, radiotherapy, or bone marrow transplantation, there is myelosuppression and immunosuppression; therefore, only the patient should be examined. Any elective oral or dental treatment should be avoided at this stage.
- A stomatological check-up should be carried out every three months during the first 12 months after cancer treatment and every six months thereafter or according to the susceptibility of each patient. At each visit it should be checked whether he is receiving immunosuppressive or myelosuppressive treatment, what his hematological status is and perform dental and oral clinical examinations, dental prophylaxis and fluoride application.
- The possible long-term sequelae of chemotherapy and radiation on the craniofacial complex should be reported. Restorative dental and periodontal treatment necessary to return the patient to optimal health should be provided at this stage, as well as symptomatic care of any residual oral lesions.
- Considerations and adaptations in the dental office.
- The patient requires in-hospital dental treatment.
- Uncontrolled patients should not be treated due to the risk of producing thromboembolic or hemorrhagic events, coronary attack or cerebral ischemia.
- Hemoconcentrated patients present tissue hypoxia, causing a delay in healing, representing a contraindication for general anesthesia, so patients with hemoglobin greater than 16g/dl and hematocrit greater than 52% should not be treated, since blood is very Viscose predisposes to the development of multiple thrombi that consume coagulation factors, increasing the risk of bleeding.
- Dental emergencies will be treated in a palliative manner, through drugs.
- In polycythemia there is a severe inflammatory response due to the increase in uric acid in the blood, so if surgical treatment (exodontics) is necessary, anti-inflammatories should be used to minimize trauma.

Conclusion

The main complications and risks of hematological conditions in the dental field were described. The main risk is that of excessive bleeding.

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