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The Importance of the Clinical Analyst in Recognizing Promyelocytes in Acute Promyelocytic Leukemia for the Patient's Prognosis

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***Abstract*—** *APL (Acute Promyelocytic Leukemia) is a very aggressive type of myeloid leukemia characterized by the marked production of promyelocytes in the bone marrow and consequently an increase in peripheral circulation, triggering numerous hemorrhagic and thrombotic events, which makes this leukemia a medical emergency requiring immediate initiation of drug treatment. The objective of this article is to demonstrate the importance of the professional in the clinical analyses in identifying these anomalous cells for the correct diagnosis and initiation of treatment, reducing the fatality of this pathology. This article addresses the onset of blood cell production, the genetic alterations that trigger acute promyelocytic cancer, as well as the complications of this pathology, the main of which is DIC (Disseminated Intravascular Coagulation), which can quickly lead to the death of the patient, being the most important factor in the urgency of drug treatment; in addition to the importance of identifying microscopic alterations in the patient's blood for the initiation of treatment and therapeutic success. The research showed that the morphological identification of these cells in clinical analyses can be critical for the initiation of treatment; as well as the administration of ATRA (all-trans-retinoic acid) - usually combined with anthracyclines or ATO (arsenic trioxide) - helps in the remission of APL and reduction of DIC cases, avoiding hematologic complications and increasing patient survival.*

I. INTRODUCTION

Blood is made up of red cells, which are responsible for gas exchange in tissues; platelets, which are responsible for blood clotting, which prevents blood loss; plasma, which contains plasma proteins, vitamins, amino acids, hormones and glucose; and the white series, which is made up of the body's defense cells, of which the leukocytes of the myeloid series include neutrophils, basophils, eosinophils and monocytes, and those of the lymphoid series, which are lymphocytes and NK (Natural Killer) cells. Promyelocytes are immature cells of the myeloid lineage that in a physiological situation would give rise to neutrophils, eosinophils and basophils (JUNQUEIRA and CARNEIRO 2017).

APL is a leukemia characterized by an increase in promyelocytes dysplastic cells in the bone marrow, causing anemia, thrombocytopenia and neutropenia . These immature cells, in addition to disrupting the normal formation of other blood cells within the marrow, are not yet functional, and, at the time of onset of symptoms, they are occupying almost all of the patient's marrow, with these

cells also appearing in the peripheral blood in large quantities (SILVA, K., [2016?] ; FREIRE et. al , 2024).

In this pathology, due to genetic errors, myeloid maturation is interrupted in the promyelocyte phase , with the vast majority of APLs being a problem involving the translocation between chromosomes 15 and 17, known as the t(15;17) translocation. This change in the gene region will alter the proteins that this cell encodes, including changes in PML (Promyelocytic Leukemia Protein), which is a tumor suppressor gene that works together with the p53 gene to suppress tumors, activating apoptosis in cells with leukemogenic potential . Another protein that will undergo changes is RAR α (Retinoic acid receptor alpha), responsible for myeloid differentiation . The production of the hybrid genes PML-RAR α and RAR α-PML will block the gene transcription that allows the maturation of these cells, due to the inability of retinoic acid to bind to the receptor, causing cancer. There are also other forms of this leukemia, all of which are generated by genetic translocation problems, always involving chromosome 17, which is responsible for the production of RAR α, but they represent only about 2% of APL cases (JACOMO, FIGUEIREDO-PONTES and REGO, 2008; LEAL, KUMEDA AND VELLOSO, 2009).

These genetic alterations result in the inability of these cells to initiate the apoptosis mechanism, and their replication in the bone marrow begins to trigger several hematological problems, such as severe anemia, neutropenia and thrombocytopenia. When they enter the peripheral blood, they can cause thrombotic events and Disseminated Intravascular Coagulation (DIC), which is considered a medical emergency (ARAÚJO, B., 2022., FREIRE et. al , 2024).

Furthermore, anomalous promyelocytes release Tissue Factor, which is the main activator of coagulation; they also have the ability to initiate the coagulation cascade through a Carcinogenic Procoagulant , causing the consumption of platelets and the formation of microthrombi in the body (GERONIMO, 2022). On the other hand, there is an increase in the formation of plasmin , which degrades fibrin, due to the increased expression of annexin A2 on the surface of promyelocytes . Annexin A2 is a receptor for plasminogen and t-PA (tissue-type plasminogen activator) that culminate in the formation of plasmin wherever these cells are circulating, causing intense hemorrhage (ALMEIDA, S., 2015).

Since the complete blood count is the fastest method for identifying these cells, as soon as confirmation occurs through cell morphology, associated with clinical suspicions, a doctor should be sought immediately to begin treatment with all-trans-retinoic acid (ATRA) or arsenic trioxide (ATO). Therefore, morphological knowledge of these cells within clinical analyses has shown to be of great importance for patient treatment (ALMEIDA, S., 2015; SILVA, K., [2016?]).

II. THEORETICAL BASIS

2.1 HEMATOPOIESIS

As reported by HOFFBRAND and MOSS (2013), in the first weeks of gestation, blood is produced mainly in the yolk sac, being derived from stem cells. From 6 to 7 months, the liver and spleen become the main hematopoietic organs, and later the bone marrow becomes the main organ to produce blood cells. During childhood and adulthood, the bone marrow becomes the only hematopoietic organ, and when the blood cells mature, they are released into the sinus spaces of the bone marrow for blood circulation.

In the first two years of age, the entire bone marrow is hematopoietic, and as the years go by it begins to be filled with fat, until in adulthood it becomes limited to the central skeleton, and the vicinity of the femur and humerus (HOFFBRAND and MOSS, 2013).

Hematopoiesis begins with pluripotent stem cells that generate mixed myeloid progenitor cells , which differentiate into other precursor cells forming erythrocytes, platelets, monocytes, neutrophils, eosinophils and basophils, and can also give rise to cells of lymphoid origin, generating B and T lymphocytes, in addition to NK cells (HOFFBRAND and MOSS, 2013).

Pluripotent stem cells proliferate and give rise to pluripotent progenitor cells , which will form blasts, which are precursor cells that present morphological characteristics of their lineage (lymphoid or myeloid), and there is also an increase in mitotic frequency. These progenitor cells give rise to other progenitor cells or precursor cells, and precursor cells give rise only to cells that are designated to mature. For the production and maturation of these cells, an adequate microenvironment and growth factors that will regulate the proliferation, differentiation, and apoptosis of immature cells are necessary, and several interleukins and cytokines are necessary . These factors influence the differentiation of the cell into its specific lineage. The release of these cells occurs by the endothelium that irrigates the bone marrow when the loss of adhesion receptors of the cells with the bone marrow occurs (JUNQUEIRA and CARNEIRO 2017).

2.2 MATURATION OF GRANULOCYTES

Granulocytes originate from a common cell called a myeloblast . When this cell begins to differentiate,

granulations appear that will be according to the lineage from which it will originate, becoming a neutrophil , eosinophil or basophil promyelocyte , then differentiating into myelocytes , metamyelocytes , rod granulocytes , and mature neutrophils, eosinophils or basophils (JUNQUEIRA and CARNEIRO 2017).

The promyelocyte is a smaller cell than the myeloblast that precedes it, with a more basophilic cytoplasm, containing granules specific to the lineage from which it will differentiate (neutrophils, eosinophils and basophils), these granules being azurophilic , and it also has a spherical nucleus that may contain a recess, and visible nucleoli (JUNQUEIRA and CARNEIRO 2017).

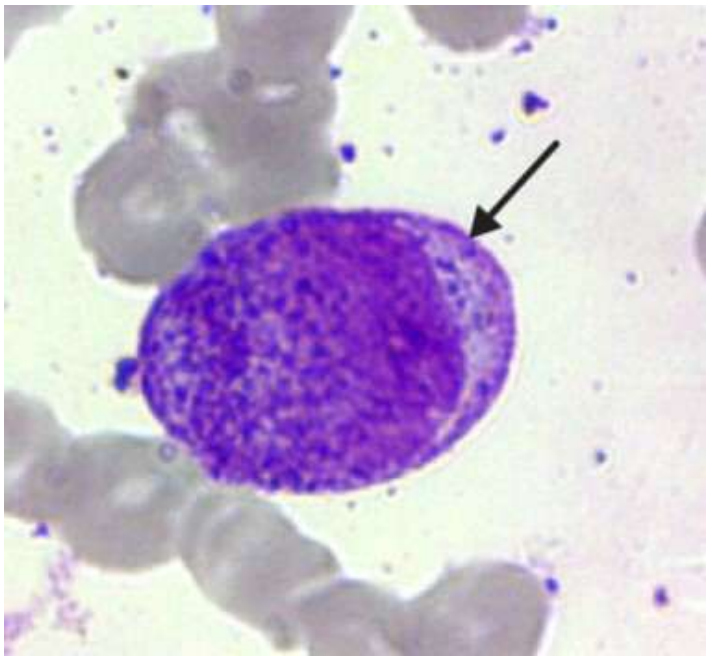

Fig.1 – Microscopic photo of a normal promyelocyte . In the image taken by microscopy, a normal promyelocyte can be seen, shown by the arrow, a cell larger than the red blood cells that are clustered around it, showing its spherical nucleus of a darker purple color, containing nucleoli, delicate chromatin and a lighter perinuclear area being the Golgi Complex, in addition to the azurophilic granules throughout the cell.

Source: *Laboratory of Clinical Analysis and Health Education (LACES),* 2017.

Maturation then proceeds to the myelocyte , containing a spherical or kidney-shaped nucleus, without cytoplasmic basophilia , and with more specific granules. The cell then transforms into a metamyelocyte , containing a deep notch in its nucleus; a rod, which is an intermediate form between the metamyelocyte and the mature cell; and finally a mature and specialized cell capable of performing its specific functions in the immune system (JUNQUEIRA and CARNEIRO 2017).

2.3 **LEUKEMIA**

Cancer is the name given to a group of more than 100 diseases in which abnormal cell growth occurs. This name was first used by Hippocrates (460 BC - 377 BC), known as the father of medicine. Unlike normal cells, cancer cells have disorderly growth, giving rise to abnormal cells. This pathology is classified as a malignant neoplasm, due to its ability to create metastases, invading other tissues, making treatment difficult and potentially leading to death (THULLER, SANT'ANA and REZENDE, 2011).

For cancer to develop, the cell needs to undergo a genetic mutation that alters its instructions, modifying its normal activities, forming anaplastic cells , without differentiation, with numerous mitoses and the ability to invade other tissues. This genetic alteration occurs in normal genes that are called proto-oncogenes , which when activated become oncogenes , becoming responsible for the formation of cancer (THULLER, SANT'ANA and REZENDE, 2011)

Leukemia is a group of diseases in which there is an exaggerated increase in the production of some blood cells, being it an acute leukemia when the affected cells are young cells, losing their differentiation (they do not transform into the cell that they would normally transform into when they mature), or chronic when the affected cells are mature, but do not perform apoptosis, which is the normal physiological process of programmed cell death, with the objective of cell renewal, destroying cells with

damaged DNA or unnecessary for the body at that time (HANNA, 2021; ARAGÃO 2015).

APL (Acute Promyelocytic Leukemia) is a subtype of AML (Acute Myelocytic Leukemia), which corresponds to the M3 and M3 variant (M3v) subtypes, in which there is an increase in blasts with promyelocyte characteristics. dysplastic , with infiltration in the bone marrow, and, as a result, these cells also appear in the peripheral blood. The increase that occurs in the bone marrow distorts normal hematopoiesis , altering red blood cells, white blood cells, platelets and, consequently, causing anemia and hemorrhages. Furthermore, these immature cells, which will be circulating in the bloodstream, are not functional and do not perform their functions as they would when they matured (PREVEDELLO and SAGRILLO, 2008; SILVA, K., [2016?]).

2.4 **GENES INVOLVED IN ALI**

Promyelocytic Leukemia or Acute Myeloid Leukemia with t(15;17) translocation is a type of leukemia that in around 98% of cases is associated with a translocation between chromosomes 15 and 17 - t(15;17) - with the break of the PML gene (Promyelocytic Leukemia Protein) on chromosome 15, and of the RARα (retinoic acid receptor alpha) on chromosome 17, encoding PML-RARα and RARα-PML hybrid proteins (JACOMO, FIGUEIREDO-PONTES and REGO, 2008; SILVA , K., [2016?]).

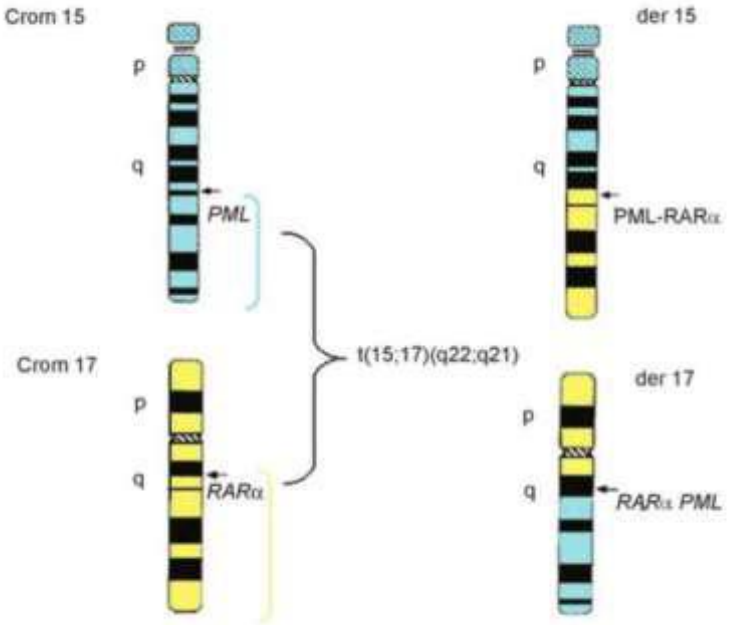

Fig.2 – Figure 2 represents the translocation between chromosomes 15 and 17 and the formation of PML-RARα and RARα-PML.

Source: LEAL, KUMEDA AND VELLOSO, 2009.

PML is a tumor suppressor gene and a regulator of p53 gene activity. This gene is known to be the most important “genome defender” gene in cancer control and is involved in most neoplasms, being activated when DNA damage occurs, stopping the cell cycle in the G1 phase and repairing DNA before duplication. Furthermore, this gene is responsible for the checkpoint from the S phase to the G2 phase and, if there is no DNA repair, PML and p53 are the genes responsible for activating apoptosis in the damaged cell. However, when a mutation occurs in p53 due to PML, both begin to induce cancer and act as oncogenes because they do not perform their basic functions, allowing genetic errors to propagate through mitosis of malignant cells (LEAL, KUMEDA AND VELLOSO, 2009; FETT-CONTE AND SALLES, 2002).

The other important gene in the occurrence of APL is RARα, which is responsible for encoding the retinoic acid receptor alpha , a nuclear hormone receptor that binds to retinoic acid-responsive elements , which is involved in the process of myeloid differentiation (LEAL, KUMEDA AND VELLOSO, 2009). Retinoids are derived from vitamin A and depend on this receptor to play their role in myeloid differentiation . Alteration of this receptor contributes to the pathogenesis of APL, leading to the blockage of differentiation in the promyelocytic phase . Retinoids are

also proliferative inhibitors and specifically stimulate the production of polymorphonuclear cells , not being observed in the differentiation of monocytes and erythrocytes, just as RARα is more expressed in this cell line (JACOMO, FIGUEIREDO-PONTES and REGO, 2008; AMARAL, 2009).

The PML-RARα gene, resulting from the translocation of genes 15 and 17, generates an oncoprotein that has lower sensitivity to retinoids and has the ability to recruit a corepressor complex, formed by: RARα; a retinoic acid X receptor (RXR); nuclear corepressor proteins Sin3a, Sin3b; histone deacetylases (HDAC) and DNA methyltransferase (responsible for methylation and inhibition of transcription), which compact the chromatin, causing the repression of gene transcription, making physiological doses of retinoic acid unable to dissociate this complex, causing the genes responsible for myeloid differentiation to be blocked, resulting in the stagnation of the cell in its maturation process in the promyelocytic phase , initiating leukemogenesis . (LEAL, KUMEDA AND VELLOSO, 2009; JACOMO, FIGUEIREDO-PONTES and REGO, 2008).

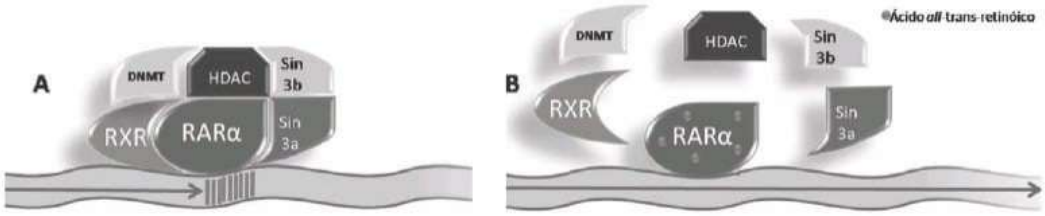

Fig.3 - Representative photo of the corepressor complex formed by the PML-RARα gene. In photo A, the complex formed by the retinoic acid receptor RARα, the retinoid X receptor , the nuclear coreceptors Sin3a and Sin3b, histone deacetylases (HDCA) and DNA methyltransferase blocking DNA transcription can be seen. In photo B, the all-trans acid can be seen. retinoic acid interacting with the RARα receptor dissociating the complex and allowing transcription.

Source: JACOMO, FIGUEIREDO-PONTES and REGO, 2008.

Both genes (PML and RARα) are part of normal hematopoiesis , while the PML-RARα hybrid gene has been demonstrated in 100% of ALI patients with t(15;17) translocation, while the RARα-PML hybrid is absent in 20%. of cases. Therefore, it is suggested that the PML-RARα gene is associated with the leukemogenesis of this leukemia (LEAL, KUMEDA AND VELLOSO, 2009).

LEAL, KUMEDA AND VELLOSO (2009) also show that, in 2% of APL cases, the RARα gene may be fused with genes other than PML, forming fusion proteins with the generic name X-RARα, which may occur on the long arm of chromosome 11 t(11;17), involving the PLZF gene (*Promyelocytic Leukemia Zinc Finger*) of chromosome 11 and RARα of chromosome 17, producing the hybrid genes PLZF-RARα and RARα-PLZF. The PLZF-RARα rearrangement is the second most common, accounting for 0.8% of cases, in addition to bringing some morphological changes, such as a more regular nucleus, an increase in cells with cytoplasmic projections, a higher frequency of CD56 expression and an intermediate morphology between AML-M2 and AML-M3. These patients with the t(11;17) translocation also presented resistance to treatment with ATRA.

CD56 is a membrane glycoprotein that appears in several hematopoietic neoplasms and is associated with poor prognosis, with a low remission rate and short survival period (JAUREGUI., 2018).

Another rarer translocation is the translocation between chromosomes 5 and 17 t(5;17); variant in which APL presents cells with the karyotype 47,XY,+22[5]/46,XY[30], forming the hybrid protein PRKAR1A-RARα, which causes PRKAR1A to lose its function of regulating gene expression. In another rare case, the patient presented a karyotype of 47,XX , t(4;17), forming the hybrid gene FIP1L1-RARα (LEAL, KUMEDA AND VELLOSO, 2009).

2.5.1 **COMPLICATIONS OF LPA**

APL causes some changes similar to other AMLs , such as neutropenia , thrombocytopenia, and anemia due to the increase in immature cells in the bone marrow. However, what causes the highest rapid mortality rate is DIC (Disseminated Intravascular Coagulation) and a state of primary hyperfibrinolysis that affects the entire nervous system and lungs (RIPOLL and MARINA, 2022). Other symptoms resulting from the decrease in functional blood cells are weakness, fatigue, infections, hemorrhages, ecchymosis (purple spots caused by blood extravasation), epistaxis (nosebleeds), and menorrhagia (heavy or prolonged menstrual bleeding) (FREIRE et. al , 2024).

Some patients, especially those with promyelocytes Hypergranular leukocytes may present few

leukocytes and rare leukemic cells in the peripheral blood. This type of leukemia has a preclinical phase of unknown duration and when it begins to be symptomatic, the patient rapidly evolves to a serious condition, presenting almost complete filling of the bone marrow by malignant promyelocytes . (FREIRE et. al , 2024).

Disseminated intravascular coagulation (DIC) and primary fibrinolysis can occur both at the beginning of diagnosis and at the beginning of chemotherapy treatment, and can cause pulmonary or cerebrovascular hemorrhage in 40% of patients, with an incidence of 10 to 20% of early hemorrhagic death, which makes ALI a medical emergency (FREIRE et. al , 2024). Pulmonary and gastrointestinal hemorrhages also occur, as well as high-fatality hemorrhagic events, such as intracranial hemorrhages (ARAÚJO, B., 2022).

Thrombotic events were also evidenced in APL, with thrombosis of deep veins, cerebral veins, hepatic portal veins, peripheral arteries, acute myocardial infarction and ischemic stroke. Thrombotic events occur in approximately 10% of cases and, because they are less evident, have a less known pathogenesis (ARAÚJO, B., 2022).

2.5.2 DISSEMINATE INTRAVASCULAR COAGULATION

According to GERONIMO, 2022:

> DIC is a disorder characterized by hemorrhagic and thrombotic phenomena. It involves systemic activation of the coagulation system, resulting in the consumption of coagulation factors, leading to multiple and uncontrollable bleeding due to blood incoagulability and hemorrhagic diathesis, in addition to multiple organ dysfunction due to compromised blood supply to the organs due to the presence of microthrombi in the circulation.

This disorder can manifest itself in both acute and chronic forms, with fibrinolysis predominating in the acute form, causing intense, prolonged bleeding, with the formation of fibrin microthrombi , consumption of platelets and coagulation factors. On the other hand, in chronic DIC, hypercoagulation or hyperfibrinolysis prevails (GERONIMO, 2022).

The anomalous promyelocytes of this leukemia release Tissue Factor (also called thromboplastin, the main activator of coagulation), Cancer Procoagulant (a cysteine - proteinase that activates Factor X without the need for Factor VII) and microparticles that activate the coagulation cascade, forming hypercoagulation (ALMEIDA, S., 2015; FRANCO, 2001).

In a normal situation, the clot is formed after plasma proteases interact with their cofactors, and a cascade of reactions occurs, forming an enzyme called thrombin, causing proteolysis that transforms soluble fibrinogen into insoluble fibrin. In 1964, a model of the coagulation cascade was proposed by Macfarlane and Davie & Ratnoff , which shows the coagulation cascade being formed by an intrinsic or extrinsic pathway (FRANCO, 2001).

In the intrinsic pathway, Factor XII is activated after the blood comes into contact with something external with a negative electrical charge. This activation is called “contact activation,” and other components in the plasma are required, such as prekallikrein (serine protease) and high molecular weight cysninogen . The cascade begins with prekallikrein and cysninogen transforming Factor XII into Factor XIIa , activating Factor XI, which activates Factor IX and, in the presence of Factor VII, activates Factor X, where the two pathways meet (FRANCO, 2001).

In the extrinsic pathway, plasma Factor VII, in the presence of its cofactor, tissue factor (or thromboplastin), activates Factor X. Factor X is the part of the reaction in which the two pathways meet, subsequently generating Factor IIa (also called thrombin), capable of converting fibrinogen into fibrin. (FRANCO, 2001).

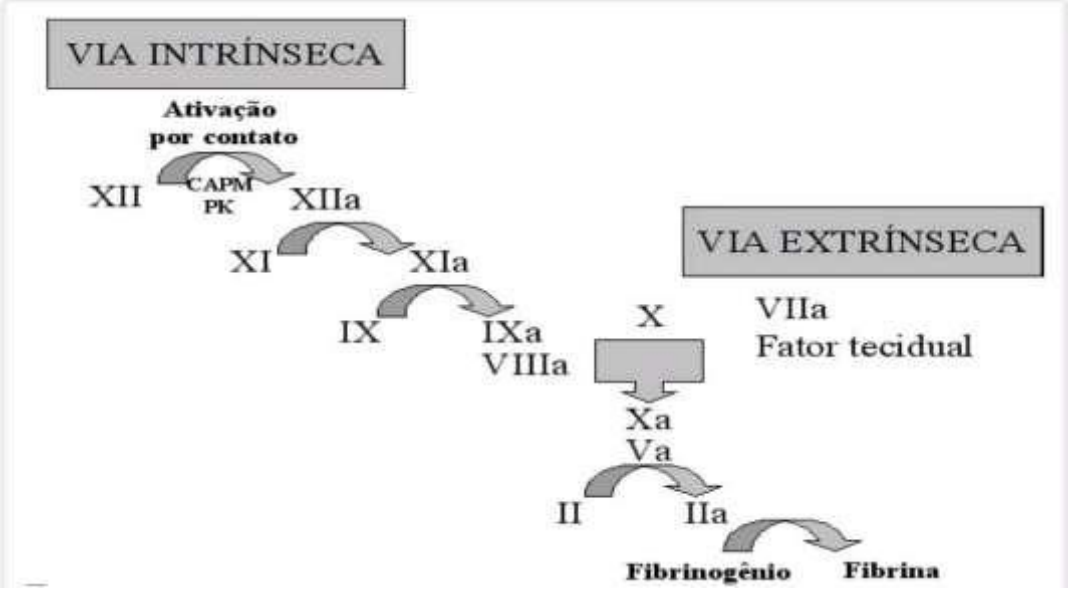

Fig.4 – Representation of the coagulation cascade model proposed by Macfarlane and Davie & Ratnoff in 1964.

Source: FRANCO, 2001.

Hyperfibrinolysis in this leukemia occurs due to elevated levels of t-PA (tissue-type plasminogen activator) and u -PA (urokinase-type plasminogen activator) that bind to the u-PAR receptor (urokinase-type plasminogen activator receptor), activating plasminogen , and eventually forming plasmin . Cancer cells have abnormal expression of annexin A2 (plasminogen and t-PA receptors) on the cell surface, which, together with increased t-PA, causes fibrinolysis wherever the cells pass, making the fibrinolytic activity of this cancer proportional to the number of circulating promyelocytes , that is, the greater the number of these leukocytes, the greater the fibrinolytic activity (ALMEIDA, S., 2015).

anticoagulation process occurs together with the coagulation process in order to balance the organism and prevent the occurrence of thrombi. This process aims to degrade the final product of the coagulation cascade: fibrin. t-PA (tissue-type plasminogen activator) and u-PA (urokinase-type plasminogen activator) are two physiological plasminogen activators that, when bound to plasminogen , cause hydrolysis of a peptide bridge , forming plasmin : a serine protease capable of degrading fibrin, thus removing the clot (FRANCO, 2001).

Plasminogen Activator Inhibitor), with PAI-1 being the main inhibitor, acting directly on plasmin (FRANCO, 2001). In APL, there is a decrease in PAI-1, reducing the levels of the main fibrinolysis inhibitor , allowing the reaction to occur for longer. Another aggravating factor is the consumption of alpha-2-antiplasmin, which is also a primary plasmin inhibitor , contributing to the occurrence of DIC (GERONINO, 2022; COSTA, 2016).

2.6 **DIAGNOSIS**

The first step in diagnosing APL is to assess the clinical symptoms, which may include pallor, hepatomegaly , splenomegaly, lymphadenopathy , fever, pharyngitis, petechiae , bone pain, gingival hypertrophy, skin infiltrations, among others. Peripheral blood and bone marrow examinations should also be performed, and the blood count will show some changes, such as low platelet count, leukocyte count <1,000 µl to 200,000 µl, neutropenia with the presence of blasts, normochromic and normocytic anemia (SILVA, G. et al. 2006).

In the laboratory, when using automation in hematology, it is important to be aware of the flags , which are warnings from hematological counters that indicate some abnormality in the blood sample, making it necessary to perform manual analysis using the blood smear, since only with microscopy can an accurate differentiation of leukocytes be made, in addition to identifying other abnormalities. The staining to be used is very important for the correct evaluation of these changes, with the most commonly used method being Giemsa with May- Grunwald , which better preserves the characteristics of leukocytes (SHÜTZLER., 2022)

Cellular morphology is the most important test for the diagnosis of APL. However, some cytochemical stains can be used to assist. For example, myeloperoxidase and Sudan Black B, which confirm that the stained cells are of myeloid nature , are specific for granulocytes and

monocytes, and reveal auer rods . Another test that has become essential for diagnosis is the immunophenotyping test , which uses monoclonal antibodies against specific epitopes of cellular antigens (SILVA, G. et al. 2006).

However, knowing that APL is a medical emergency, which is fatal in the absence or delay of appropriate treatment, treatment should be started immediately after clinical suspicion and some diagnostic test, such as a blood count (which is the fastest method), allowing advance notification to the physician, who will start the treatment. Other tests, such as immunophenotyping , can take 3 to 4 days to obtain the result; the myelogram , 2 to 5 days; cytogenetics , 11 to 22 days, and this waiting time can cause the patient's death (SILVA, K., [2016?]).

According to ALMEIDA, S. (2015), the first 24 hours are critical for diagnosis. Mortality from this disease can reach 55% in the first month due to the hemorrhagic condition. All-trans-retinoic acid (ATRA) or Arsenic Trioxide (ATO) should be administered as soon as possible, and analysis of the morphological aspects of the cells will be a sufficient indication to begin treatment, even before genetic confirmations.

Thus, the importance of the professional in knowing the morphological characteristics of promyelocytes in APL is elucidated. These cells can present in two different main forms in this leukemia (hypergranular form and hypogranular form), presenting different characteristics in promyelocytes . There are also rarer forms, such as the hyperbasophilic form and the variant associated with the PLZF-RARα fusion (SILVA, K., [2016?]).

The classic form, also called hypergranular , presents an eccentric, dysmorphic nucleus , with an ill-defined border and a dark hue due to the cytoplasmic granules that prevent its clear visualization. The granulation is exuberant, azurophilic and there are often auer rods organized in bundles, naming the cells with the presence of this inclusion: "*faggot ". cells ".* Auer rods (or auer bodies) are indicators of acute myeloid leukemias and are possibly of lysosomal origin , being important for identifying myeloid syndromes in general, being present in APL (also called Acute Myeloid Leukemia M3) (ALMEIDA, S., 2015; SILVA, K., [2016?] ; HANNA, 2021; GALIACHO et al., 2022).

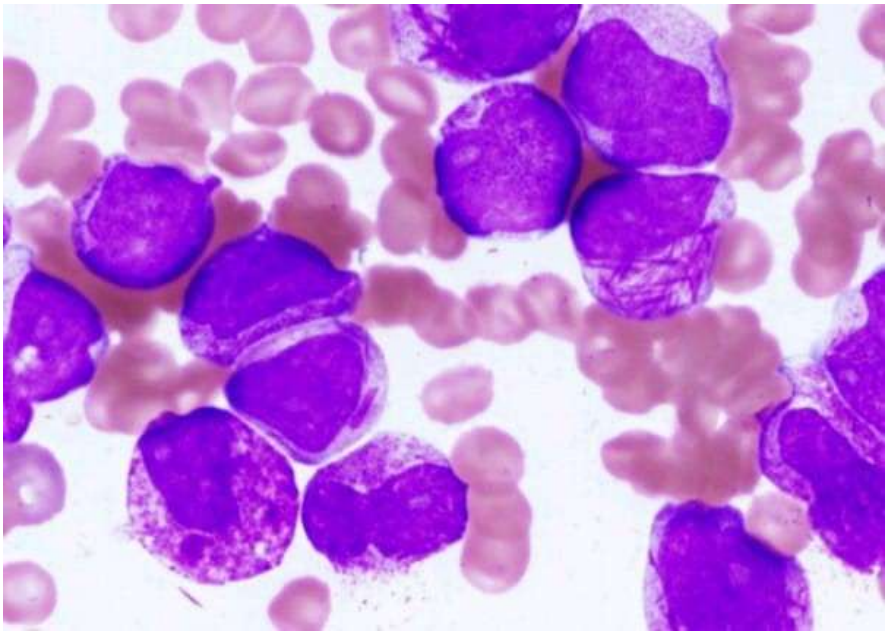

Fig.5 – Microscopic image of promyelocytes in LPA in their hypergranular form .

SOURCE: SILVA, K., [2016?] .

The hypogranular or microgranular form has more discreet cytoplasmic granulation, the nucleus is more visible and clearer compared to the hypergranular form, presenting a bilobular shape , with rare auer rods (SILVA, K., [2016?] ; HANNA, 2021).

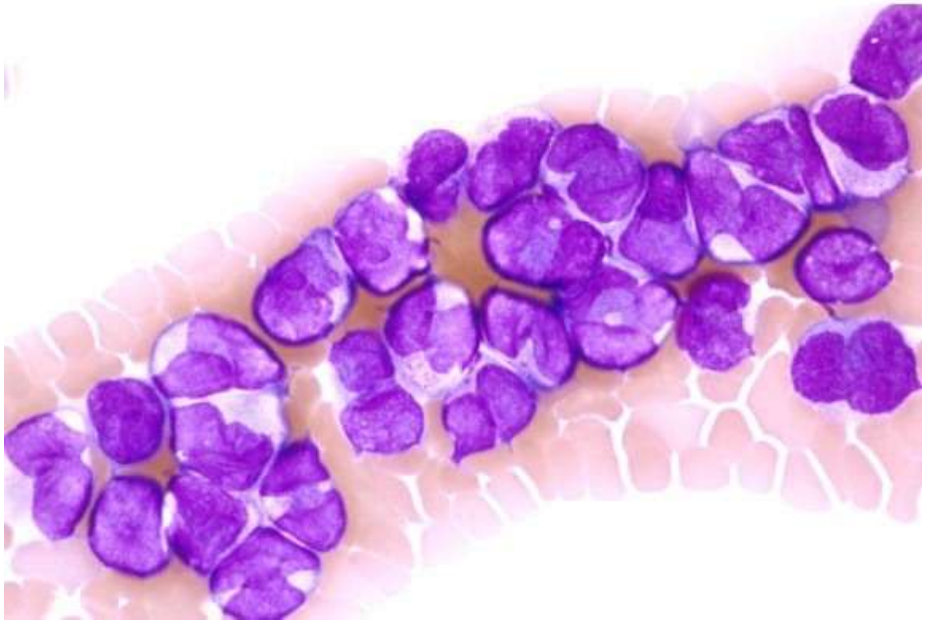

Fig.6 – Microscopy image of promyelocytes in LPA in their hypogranular form .

Source: SILVA, K., [2016?]

Of the rare forms, the basophilic form has a high nucleus/cytoplasm ratio, strongly basophilic granules , and does not have auer rods. On the other hand, the PLZF-RARα form has a regular nucleus with condensed chromatin, fewer granules than the hypergranular form , and rare auer rods (ALMEIDA, S., 2015).

2.7 **TREATMENT**

Due to the possibility of hematological complications and the rapid progression of the disease, as soon as the diagnosis is made, it is necessary to immediately begin treatment with all-trans-retinoic acid (ATRA), which has a similar role to retinoids in the maturation of these promyelocytes . It is important to highlight that, due to its mechanism of action, ATRA may not be effective in the rarer forms of ALI (SANTANA, 2019; KOTOWSKI, MONTEIRO, ARAÚJO, M., 2007).

ATRA, together with anthracycline and cytarabine (Ara-C), or associated with ATO, proved to be effective in remitting ALI in an estimated 95% of cases. ATRA, as it is a natural metabolite of retinol and belongs to the class of retinoids , binds to the retinoic acid receptor α (RARα), as if it were a supraphysiological dosage of retinoic acid , having an inhibitory effect on both the PML gene and the RARα gene. . It is responsible for the dissociation of the corepressor formed by RARα, the retinoic acid X receptor (RXR), the nuclear corepressors Sin3a and Sin3b, histone deacetylases (HDAC) and DNA methyltransferase . With this dissociation, the transcription block is undone and the cell is able to carry out gene transcription, leading to the complete maturation of the promyelocyte and also inducing its apoptosis (SANTANA, 2019; KOTOWSKI, MONTEIRO, ARAÚJO, M., 2007).

ATRA will only have a good response in patients who have the t(15;17) translocation, due to its mechanism directly related to the RARα receptor and PML. Furthermore, this drug does not act on the leukemic clone, and it is necessary to combine it with chemotherapy to induce complete remission of the cancer (KOTOWSKI, MONTEIRO, ARAÚJO, M., 2007).

Retinoic Acid Syndrome , also called Differentiation Syndrome (DS), which has symptoms such as fever, dyspnea, respiratory problems, pulmonary infiltration, hyperleukocytosis , pleural effusion, renal and hepatic failure, and multiple organ failure. Regarding the cardiac problems of this syndrome, pericardial effusions, chest pain, peripheral edema, and hypotension can also be triggered. Associated chemotherapy helps to reduce the incidence of this syndrome. Studies suggest that this syndrome can also occur with the use of ATO (SOUZA., [2012?] ; SANTANA, 2019)

Until 1992, the use of anthracyclines was the first-line treatment for APL, and although there was a good remission rate, many deaths from DIC occurred. After the arrival of ATRA , anthracycline treatment associated with all-trans-retinoic acid began (SOUZA., [2012?]).

APL cells have little expression of P-glycoprotein, which promotes the efflux of chemotherapeutic agents, preventing this type of medication from acting on the cell.

With the absence of this glycoprotein, promyelocytes become more susceptible to the action of anthracyclines , with idarubicin being the anthracycline used because it can intercalate into DNA, interact with Topoisomerase II, and inhibit nucleic acid synthesis in bone marrow and blood cells (SOUZA., [2012?] ; HUBER, MARUIAMA and ALMEIDA, W, 2010, KOTOWSKI, MONTEIRO, ARAÚJO, M., 2007). In the case of cytarabine , its role has not yet been well defined and, in some cases, its absence in the treatment does not cause a negative impact (ALMEIDA, S., 2015).

trioxide (ATO) is used in cases where the patient has recurrence of the disease after treatment with ATRA, and is also an alternative medication for patients who cannot undergo chemotherapy, due to its lower toxicity. In small doses, ATO degrades PML-RARα transcripts and indirectly activates caspases , which will lead to cell apoptosis, without needing to use the same pathways as ATRA. Caspases are enzymes that are inactive in the cell, but when activated, they initiate cell degradation, that is, they are the enzymes responsible for initiating apoptosis . Its name refers to the “C” for cysteine , “ asp ” for aspartate and the enzyme ending “ase” (SANTANA, 2019; KOTOWSKI, MONTEIRO, ARAÚJO, M., 2007; ARAGÃO, 2015). When combined with ATRA, ATO causes synergistic regulation of telomerases , causing telomere shortening , leading to promyelocyte cell death (SANTANA, 2019).

III. METHODOLOGICAL PROCEDURES

This work was carried out based on a review of the scientific literature on the subject. The main research sources were SciELO (*Scientific Electronic Library Online*) and the Google Scholar tool. To develop this research, keywords and terms such as “LPA”, “ acute promyelocytic leukemia”, “disseminated intravascular coagulation”, “ all-trans acid” were used. retinoic ”, “blood count”, “ anomalous promyelocytes in APL”, “PML RARα”, “morphology of APL”, “ hematopoiesis ”, “cancer”, “slide staining”, “treatment of APL”, etc. Scientific articles, meta-analyses, books and monographs relevant to the subject addressed were used.

IV. RESULT AND DISCUSSIONS

According to the authors referenced in this research, APL is an anemia that begins its symptoms very aggressively, and can quickly evolve into DIC, causing a severe hemorrhagic condition that can quickly lead to the patient's death. DIC is directly formed by anomalous promyelocytes and the circulating quantity will influence the severity of the condition.

It has also been demonstrated that the maturation of these cells is interrupted in the promyelocytic state due to a genetic mutation that prevents them from continuing the maturation process. Thus, research has shown the need to use ATRA or another medication that will cause these cells to continue their maturation or undergo apoptosis, which will drastically reduce DIC cases by reducing the number of circulating promyelocytes .

Another point validated in this research was the importance of the blood count for the treatment of this leukemia. The blood count was presented as the fastest test to validate this pathology, and although it requires other confirmations that take longer, the symptoms of this disease and the appearance of these cells on the patient's slide are already sufficient reasons to start the APL treatment protocol, due to the aggressiveness of this leukemia.

Therefore , given the points highlighted so far, such as the characteristics of these cells in the slide and other classic leukemia alterations, the inclusions that indicate myeloid leukemia and pathognomonic characteristics of this disease (such as the bilobed nucleus of promyelocytes) are already sufficient for the start of treatment, which demonstrated high remission when started quickly.

V. FINAL CONSIDERATIONS

Analyzing the data found in the research, it was found that APL is an oncological pathology that has proven to be very aggressive, with a high mortality rate due to its complications caused by the DIC condition, which can cause hemorrhages and blood clots throughout the body. It was also demonstrated how the medications used to treat this leukemia contribute to the remission of the disease, reducing the cancer cells in the peripheral blood and reducing the chances of this anemia presenting its most severe state, considerably increasing the patient's survival.

However, its rapid evolution demands attention from all professionals involved, from the suspicion of cancer by the doctor who treated the patient, to the drug and chemotherapy treatment, being crucial that the doctor identifies the signs and symptoms of leukemia and quickly requests the patient's blood count, which will contain classic changes of leukemia, such as anemia, thrombocytopenia and neutropenia .

Upon arrival at the analysis laboratory, it is up to the clinical analyst to recognize the classic changes in APL, such as the cellular patterns of the blasts in this leukemia (both in its hypergranular and hypogranular forms , in addition to the rare forms), as well as to recognize the classic inclusion of myeloid leukemias that will contribute

to the clinical diagnosis. It is immediately the analyst's responsibility to contact the physician and inform him/her that the slide is suggestive of APL, collaborating with the immediate start of treatment, which allows the reduction of the DIC condition and can contribute to a better prognosis for the patient.

Therefore, according to the study, it is imperative that the clinical analyst knows how to identify the anomalous promyelocytes in APL as quickly as possible, because the complete blood count is the first step in suspecting any leukemia and, consequently, will be the first choice test (in addition to being the quickest and most accessible to be performed). Since APL is a medical emergency, genetic confirmation should not be expected to begin treatment; only the analyst's confirmation of the type of cell presented on the slide is sufficient to begin the APL treatment protocol, highlighting the importance of this professional in the patient's prognosis.

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