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MYELODYSPLASTIC SYNDROMES

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ABSTRACT

Introduction: Myelodysplastic syndrome is a pathology characterized by its hematopoietic, pluripotential ineffective process in the bone marrow, i.e. causing dysplasia in at least one of its hematopoietic lines with functional and morphological alterations, which, at some point may evolve into leukemia.

Objective: review, analyze and describe the most notable features of myelodysplastic syndromes.

Methodology: A total of 20 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 11 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed, SciELO, Google Scholar, Medigraphic and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: myelodysplastic syndrome, hematopoietic, anemia, leukemia.

Results: It is estimated to have an incidence of 4-12 conditions out of 100 000 patients per year, and it can reach up to 30 out of 100 000 in individuals older than 70 years of age. The occurrence of this anomaly in pediatric age and in young adults is rare and infrequent, and a certain predominance in the male sex has been reported, with a ratio of 1:5, and no relationship with race has been found. Most patients develop symptomatology related to cytopenias and anemia; isolated neutropenias and thrombocytopenias also occur, although not less frequently.

Conclusions: Myelodysplastic syndromes are highly complex disorders of low incidence. They mainly affect the production of hematopoietic stem cells, being disorders of difficult approach, due to the mutation and the affection that these disorders entail, triggering aggressive dysplastic and blood diseases such as anemias and leukemias, which makes therapeutic decisions difficult, so it is extremely important to make a correct diagnosis based on a clinical, morphological and exclusion analysis. In addition, the patient's condition and age must be taken into account, so that the treatment is effective and the patient's survival is adequate.

Keywords:MDS:Myelodysplastic syndrome.

Hematopoietic Process: The process of cell production,involving cell proliferation, differentiation, and maturation.

Leukemia: a malignant condition involving excessive production of immature or abnormal white blood cells, ultimately suppressing the production of normal blood cells and producing symptoms related to cytopenias.

Cytopenia: Lower than normal blood cell count.

Acute Myeloblastic Leukemia: Malignant transformation and uncontrolled proliferation of a myelocytic progenitor cell with abnormal differentiation and prolonged survival results in high numbers of circulating immature blood elements and replacement of normal bone marrow by malignant cells.

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INTRODUCTION

Myelodysplastic syndrome is a pathology characterized by its hematopoietic, pluripotential ineffective process in the bone marrow, that is, causing dysplasia in at least one of its hematopoietic lines with functional and morphological alterations, which, at some point can evolve into leukemia thus becoming a pathology of difficult clinical approach(1).

All this causes patients diagnosed with MDS to present with frequent anemia, risk of infection and hemorrhage (depending on cytopenia), as well as a variable tendency of transformation to acute myeloblastic leukemia. Therefore, they can be classified as primary MDS; without a cause, and secondary MDS caused by exposure to chemotherapy, radiation, or toxins such as benzene and its derivatives(2,3).
Usually 80% of cases occur in elderly patients, from 60 years of age onwards, and very infrequently in young patients or young adults. The median age at diagnosis is over 65 years; data from the Spanish MDS Registry confirm that the median age at diagnosis is 75 years, with 80% of patients being over 60 years of age, with a clear predominance of males(1,2).

METHODOLOGY

A total of 20 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 11 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed, SciELO, Google Scholar, Medigraphic and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: myelodysplastic syndrome, hematopoietic, anemia, leukemia.

The choice of literature presents elements related to an overview of Myelodysplastic syndrome.

DEVELOPMENT

Previously myelodysplastic syndromes were known as pre leukemia, refractory anemia or latent leukemia. Nowadays the term "myelodysplastic syndromes" refers to a type of blood cancer caused by bone marrow failure, meaning that the bone marrow does not produce a sufficient amount of healthy blood cells, on the other hand, as soon as they are produced, the blood stem cells and bone marrow are altered, becoming abnormal and generating genetic changes or mutations.

In the population the blast cells constitute less than 5% of all bone marrow cells, they are called the immature cells of the bone marrow, so it leads to a determining factor in the severity of myelodysplastic syndrome, while the blast cells are elevated indicates that the disease has progressed even at that point, to become an acute myeloid leukemia(1,2).

It is known that there are different types of myelodysplastic syndromes, so its diagnosis must be very careful, that is to say, clinical, morphological and exclusion analysis, processes associated to reversible dysplasia must be discarded such as deficit of maturative factors, infection by diverse viruses, action of cytotoxic agents, heavy metals, association to chronic hepatopathy or to another type of neoplasia(1,2).

Considering that myelodysplastic syndrome is a progressive and severe disease, it can manifest itself with recurrent anemia, i.e. a very rapid or very slow decrease of healthy red blood cells in the blood. In addition, there are other clinical manifestations that the patient may present together with anemia. The specialist physician should classify this disease as it is of utmost importance for its clinical management(1,2).

In 1900 Leube described a patient with severe macrocytic anemia with evolution to acute leukemia, from this case arose cases with macrocytic anemia, cytopenias, maturational alterations of myeloid precursors, increased blasts and risk of evolution to leukemias. From the cases that were presented, in 1953 the term "Refractory Anemias" was applied to a well-defined group, but in 1970 Saarni and Linman, after research carried out during that period, recognized the disease as a primary bone marrow disorder caused by decreased maturation of hematopoietic precursors and bone marrow hypercellularity. In the same year an international group of pathologists called Franco-American-British (FAB) conducted an in-depth study, so that in 1976 the term Myelodysplastic Syndromes was coined with two subgroups: Chronic Myelomonocytic Leukemia (CMML) and Refractory Anemia with Excess Blasts (AREB).

Mora, determines that the most used chemotherapy was 5-azacitidine, followed by lenalidomide and decitabine.
In 1980 the classification was investigated in depth and later in 1982 it was published by the FAB group, based on morphologic criteria with five subgroups: refractory anemia (RA), refractory anemia with ring sideroblasts (ARSA), refractory anemia with excess blasts (AREB), refractory anemia with excess blasts in transformation (AREB-t) and chronic myelomonocytic leukemia (CMML), this classification is still valid and was the basis for the WHO 2002 classification, revised in 2008, which combines morphology, cytochemistry and cytogenetics(1,2,3).
The 2008 classification includes refractory cytopenia with unilineage dysplasia (CRDU) or with multilinear dysplasia (CRDM), depending on the blast cell count in bone marrow and peripheral blood, and 5q syndrome with anemia and thrombocytosis, which has a very good response to lenalidomide.

Since then, the WHO classification has been updated twice, once in 2008 and again in 2016(1,2,3).
Since the WHO classification is still maintained, the clinical manifestations depend on cytopenias arising from chronic marrow failure with anemic syndrome and/or hemorrhagic manifestations and/or increased infections. The most common cytopenia is anemia.

Within the laboratory tests the parameters of values that refer to cytopenias are hemoglobin less than 10, neutrophils below

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1800/mm3 and platelets less than 100,000/mm, some degree of thrombocytopenia is usual; in the peripheral smear, platelets vary in size, and some appear hypogranular. Patients with refractory sideroblastic anemia may present with thrombocytosis in combination with the JAK2 V617F mutation(2).

When assessing laboratory parameters very carefully, it should be known that the leukocyte count may be normal, high or low. The granularity of the neutrophil cytoplasm is found to be low, with anisocytosis and variable numbers of granules or sometimes no granules. Eosinophils may also show abnormal granulation(2,3).

An abnormal increase in blood monocytes is characteristic of the subgroups of chronic and juvenile myelomonocytic leukemias. Immature myeloid cells may also be found, but can be seen within the features of the less differentiated subgroups. The cytogenetic pattern is usually abnormal, with one or more clonal cytogenetic abnormalities usually involving chromosomes five or seven(2,3).

In 80% of the population, in patients with myelodysplastic syndrome, a mutation can be detected with different variabilities of mutated genes that can lead to different clinical or laboratory manifestations as explained above. The 5q deletion is a unique form of myelodysplastic syndrome in women with macrocytic anemia and thrombocytosis, but, there are other genes that are usually mutated in patients with myelodysplastic syndromes: TET2, SF3B1, ASXL1, DNMT3A, SRSF2, RUNX1, TP53, U2AF1, EZH2, ZRSR2, STAG2, GBL, NRAS, JAK2, SETBP1, IDH1, IDH2 and ETV6(2).

Prognosis is determined by the percentage of blast cells in both bone marrow and peripheral blood, cytogenetics, and the number and degree of cytopenias. Cases with an increased percentage of blasts are at higher risk of progressing to AML, and therefore have a worse prognosis. Genetic analysis has shown that there are alterations that have a better evolution, such as isolated chromosome loss and isolated deletion of chromosome 5q, 20q, 12q and 11q; however, 7q deletion, trisomy 8 and complex anomalies have a worse prognosis(3,4).

With all this analysis it is known that not all MDS require immediate or equal treatment, that is to say, in those of low risk, in which an increase of apoptosis mechanisms predominates leading to refractory cytopenias, the quality of life must be improved with growth factors such as erythropoietin and granulocyte growth factor (G-CSF) trying not to induce transfusion dependence and administering transfusion support only when required(4,5,6).

If the proliferative tendency towards acute myeloid leukemia predominates, the objective of treatment is to improve survival with the administration of hypometalines such as lenalidomide, azacitidine or decitabine, trying to reduce transfusion dependence and if necessary with the administration of intensive chemotherapy, achieving remission in selected cases(5,6).

Most of the research carried out since 1900 with Leube on a case of macrocytic anemia; until 1976 when the international group of French-American-British pathologists carried out certain in-depth studies demonstrating that there are certain cases with macrocytic anemia, cytopenias, maturational alterations of myeloid precursors, increased blasts and risk of evolution to leukemias. Delgadp determines that the relationship between MDS and leukemias is still a controversy that we believe will continue until all the necessary knowledge about the genetic, molecular and biological bases has been achieved. Based on this information, the WHO has published different classifications based on the cytopenias described, the 2008 classification has refractory cytopenia with unilineage dysplasia (CRDU), or with multilinear dysplasia (CRDM).

Depending on the blast cell count in bone marrow and peripheral blood, 5q syndrome is also considered as an entity with anemia and thrombocytosis, this syndrome has a very good response to lenalidomide. The most current WHO classification is maintained since 2016(7).

Among the proposed criteria the following stand out:
Agranular myeloblasts or with presence of Auer rods in 5-30 % of a total of 400 nucleated cells.

- Agranular neutrophils.
- Ringed sideroblasts.
- Karyotype alterations.

The prognosis is determined by the percentage of blast cells in both bone marrow and peripheral blood, cytogenetics and the number and degree of cytopenias(7).
Based on different investigations, a classification chart of myelodysplastic syndromes has been made.

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Table 1. CLASSIFICATION OF MYELODYSPLASTIC SYNDROMES.

CLASSIFICATION OF MYELODYSPLASTIC SYNDROMES					
Subgroup	**%**	**Sideroblasts**		**Monocytes**	**Degree of dyshemopoiesis**
	Peripheral blood	**Bone marrow**	**%**	**10*9/L**	
Refractory Anemia	<1	<5	<15	+	+
Refractory anemia with sideroblasts	<1	<5	>15	+	+
AREB	<5	5-20	Variable	+	++
AREB-t	>5	21-29	Variable	Variable	+++
Chronic myelomonocytic leukemia CMML	<5	0-20	Variable	+++	++

Source: Duarte, Y., Perez D (2021) Sindromes Mielodisplasicos Tratamiento y Clasificacion(8).

Camacho deduces that myelodysplastic syndromes are usually asymptomatic entities until very advanced stages, which leads to significant morbidity and mortality.

Complementary diagnostic studies
Clinical manifestations depend on cytopenias derived from chronic bone marrow failure with anemic syndrome and/or hemorrhagic manifestations and/or increased infections. The most common cytopenia is anemia.

Cytogenic
Karyotype alterations, considered clonal markers of malignancy, are present in 30-50% of primary myelodysplastic syndromes and in 80% of secondary myelodysplastic syndromes, none of these being specific to this entity.
A higher incidence of total or partial loss of a chromosome has been observed, followed by the existence of trisomies. Translocations are less frequent and affect mainly chromosomes 1,3,5,7 and 17(9).

Molecular
They have value in relation to the leukemogenic potential, since on many occasions cytogenetic alterations occur in areas where oncogenes and tumor suppressor genes exist. In patients with myelodysplastic syndromes, generally point mutations have been described. The most frequent mutations are those involving the RAS family, which have been identified in up to 40% of the patients studied(10).

Immunological
In patients with myelodysplastic syndrome a great variety of alterations affecting cellular immunity have been observed, such as absolute lymphopenia, with a decrease in the number of functionally immature NK cells, T cells with a decreased response to mitogen action and a significant deficiency in interferon production. Immunophenotyping studies have shown a significant decrease in CD 4+ cells with normal or increased CD 8+ cells(11).

Enzyme studies
Serum lactate dehydrogenase (LDH) levels are usually elevated and some authors have conferred independent prognostic value(11).
DeZerm deduces that people with myelodysplastic syndromes usually have a "cytopenia", i.e. a low level of one or more blood cell types.

RESULT

Patients affected by these syndromes are usually due to the degree of cytopenia present. The most frequent symptoms include fever, bleeding, and in those conditions with anemia, mild to moderate splenomegaly can be found, almost always related to the diagnosis of chronic myelomonocytic leukemia. The incidence is estimated to be 4-12 conditions out of 100,000 patients per year, and may reach 30 out of 100,000 in individuals over 70 years of age. The occurrence of this anomaly in the pediatric age and in young adults is rare and infrequent, and a certain predominance in the male sex has been reported, with a ratio of 1:5, and no relationship with race has been found. It is known that 20% are secondary to the use of antineoplastic drugs, among which alkylating agents, epipodophyllotoxins and anthracyclines, contact with chemical products, mainly those derived from benzene, exposure to ionizing radiation and more recently it has been suggested that smoking increases the risk of suffering from this syndrome. Most patients develop symptoms related to cytopenias and anemia; isolated neutropenias and thrombocytopenias are also present, although not less frequently.

The classification of myelodysplastic syndromes has been somewhat complex due to the clinical and morphologic heterogeneity of the cytopenias. A series of classification systems have been developed for these syndromes, the purpose of which has been to determine the risk of progression to acute myeloblastic leukemia (AML) and overall survival.

Its diagnosis implies a careful clinical, morphological and exclusion analysis, since processes associated with reversible dysplasia such as deficiency of maturation factors, infection by

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various viruses, action of cytotoxic agents, association with chronic liver disease or another type of neoplasm must be ruled out. It is also based on morphologic evidence of dysplasia, altered maturation on examination of the bone marrow in the myelogram and biopsy; and information obtained from other studies such as karyotyping, flow cytometry or other molecular studies. The diagnosis of myelodysplasia is complex, the patient's history, clinical history, peripheral blood and bone marrow morphology, absolute and relative values, general biochemistry, bacteriology and virology should be evaluated, and therapy should be individualized for each patient, considering age, performance status, risk groups and comorbidities.

A fundamental element in the diagnosis is the qualitative morphologic alterations in one or more hematopoietic series that appear in both peripheral blood and bone marrow and must be present in at least 10% of the cells in each of the series.

The diagnosis of these syndromes is made by exclusion, so it is necessary to rule out the existence of a group with similar morphological characteristics before establishing the diagnosis. These include nutritional anemias due to vitamin B12, folic acid and pyridoxine deficiency, bone marrow aplasia, etc.

Over time, different studies based on clinical evidence and research studies have been carried out, suggesting different classification tables, as it has been observed that the degree of affection depends on several factors, both the result of clinical analysis and the evolution of the patient affected with the pathology.

The objective of treatment is to improve survival with the administration of hypomethylating agents such as azacitidine or decitabine, trying to reduce transfusion dependence and if necessary with the administration of intensive chemotherapy achieving remission, to seek cure with allogeneic transplantation of hematopoietic precursor cells, according to the functional state and age of the patient.

CONCLUSIONS

Myelodysplastic syndromes are highly complex disorders of low incidence. They mainly affect the production of hematopoietic stem cells, being disorders of difficult approach, due to the mutation and the affection that these disorders entail, triggering aggressive dysplastic and blood diseases such as anemias and leukemias, which makes therapeutic decisions difficult, so it is extremely important to make a correct diagnosis based on a clinical, morphological and exclusion analysis. In addition, the patient's condition and age must be taken into account, so that the treatment is effective and the patient's survival is adequate.

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