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Research Paper

Myelodysplastic syndromes Experience of the laboratory of the Hassan II University Hospital of Fez (in the era of the new WHO 2016 classification) About 18 cases.

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Abstract:
The myelodysplastic syndromes (MDS) are a very heterogeneous group of haemopathies commonly encountered in hematology. The MDS are clonal disorders of pluripotent stem cells or myeloid characterized by ineffective hematopoiesis responsible for blood cytopenias that contrast with a generally rich marrow. Descriptive epidemiological studies on MDS are few.This is a disease of the elderly whose frequency is probably underestimated. Its diagnosis is sometimes difficult because of the borders between forms of different types of SMD, between SMD and myeloproliferative syndrome or other causes of medullary dysplasia and because of the large variability of clinical presentation. The MDS is rare in children, they can be acquired primitive, or associated with constitutional anomalies or secondary to a treatment.

Keywords: *myelodysplastic syndrome, WHO2016 classification, IPSS-R prognostic classification.*

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I. Introduction:

Myelodysplastic syndromes encompass a heterogeneous range of chronic and clonal conditions affecting hematopoietic strains. They are characterized by abnormal proliferation of bone marrow precursors with an increased rate of apoptosis, resulting in inefficient hematopoiesis responsible for peripheral cytopenias with a generally hyperplastic or preserved rich marrow. They are also called pre-leukemic states due to the risk of progression to acute myeloid leukemia (AML) in one third of cases [1].

They have a very heterogeneous clinical presentation, the anemic syndrome represents the dominant clinical feature, but the discovery is made in an incidental way in half of the cases on the occasion of a checkup or to explore another condition.

The WHO 2016 classification subdivides MDS into several subtypes, based on morphological criteria (number of cytopenias, number of dysplastic lineages, percentage of marrow blasts and percentage of sideroblasts in crowns) and cytogenetic study (marrow karyotype) [2].

The evolution is variable and can be progressive with increasing cytopenias and/or bone marrow blastosis, or quite abrupt with transformation in a few weeks from a relatively stable myelodysplastic syndrome to AML. Nevertheless, the evolution of MDS is unfavorable and the median survival ranges from 9 months to more than 8 years depending on the initial risk category. The main causes of death are infections and bleeding (50-60%), as well as transformation to acute leukemia (20-30%) [3].

A better knowledge of the pathology on the part of practitioners could contribute to an early diagnosis. In this work, we collected data on 18 cases of MDS in patients hospitalized at the Hassan II University Hospital in Fez. The aim of this work is to analyze the epidemiological data on the characteristics of the population, on the mode of discovery of MDS in its clinical and biological presentation, on the mode of therapeutic management and on the evolution.

II. Material and Methods:

This is a retrospective study spread over 3 years from January 1, 2018 to December 31, 2020, carried out in the hematology department of the CHU HASSAN II of Fez, focusing on the epidemiological, clinico-biological, therapeutical and evolutionary profile. The study included patients hospitalized in internal medicine and whose diagnosis of MDS was retained. Based on clinical presentations, cytopenias, cytological abnormalities on blood smear and myelogram, and cytogenetic abnormalities on bone marrow karyotype, and for patients with dysmyelopoiesis secondary to a deficiency (vitamin or other), incomplete or lost to follow-up records were excluded

The information was collected by studying the medical files and on pre-established operating sheets covering: the epidemiological aspect, the clinical presentation (history, clinical signs, etc.), and the paraclinical assessment. We performed, for all patients, blood smears and medullary smears stained with May-Grunwald-GIEMSA and the reading is done with an optical microscope with objective (×10, ×20, ×100), for some patients a medullary karyotype was performed.

III. Results:

During this period, we diagnosed 18 cases of MDS in patients with a mean age of 66 years with extremes ranging from 29 to 91 years. These patients were mainly women, 13 women or 72.2% and 5 men or 27.8%. The sex ratio M/F is therefore 0.38. In our series, 94.4% of the patients had primary MDS for which no causal factor was found and only 5.6% had MDS secondary to chemotherapy . No cases of an exposing occupation n´ were found. Ten patients had no specific pathological history.

However 44.4% (nb=8) had comorbidities such as diabetes in 37.5% (nb=3) or hypertension in 25% (nb=2) or combination of hypertension and diabetes in 25% (nb=2) or autoimmune disease or heart disease in 12.5% (nb=1). In our series, three patients had no symptoms related to MDS and were discovered following the existence of biological abnormalities during a systematic workup.

Clinical manifestations:

The anemic syndrome associating dyspnea of effort, cutaneous-mucosal pallor and asthenia, represents the clinical element the most found in 15 patients (83%).Then comes the hemorrhagic syndrome in 38% of the cases (n=7) made of ecchymoses, gingivorrhages or epistaxis. Next, the infectious syndrome in 6 patients (33%). Finally, the tumor syndrome was least found in 3 patients (16%).

Biological results:

1. **Hemogram**

Anemia is the most frequent cytopenia in our case series, present in 88.8% of patients (nb=16), followed by thrombocytopenia, found in 55.5% of cases (nb=10) and finally leukopenia in 38.8% of cases (nb=7). Isolated cytopenia was found in 51% of cases. Isolated anemia was present in 50% of cases (nb=9), thrombocytopenia in 11% of cases (nb=2) and isolated leukocyte lineage damage was very rare in 5% of cases (nb=1). Bicytopenia was present in 22% of cases, and pancytopenia in 27% of cases. In our series, the average hemoglobin level is 8.6 g/dl with extremes ranging from 4.3 g/dl to 12.3 g/dl. Normocytic anemia is more frequent (80%), followed by macrocytic anemia (18%) and microcytic anemia (2%). More than 90% of anemias are normochromic with a mean corpuscular hemoglobin concentration (MCHC) between 32 and 38, only 10% are hypochromic.

2. **Blood smear**

The blood smear examination showed hypogranulation and hyposegmentation of polynuclear cells
Neutrophils (pseudo-Pelger type abnormalities) in 85% of cases. Other cytological abnormalities were anisopoikilocytosis, macrocytes, Jolly bodies, platelet anisocytosis, macroplatelets and giant platelets in 61% of cases.

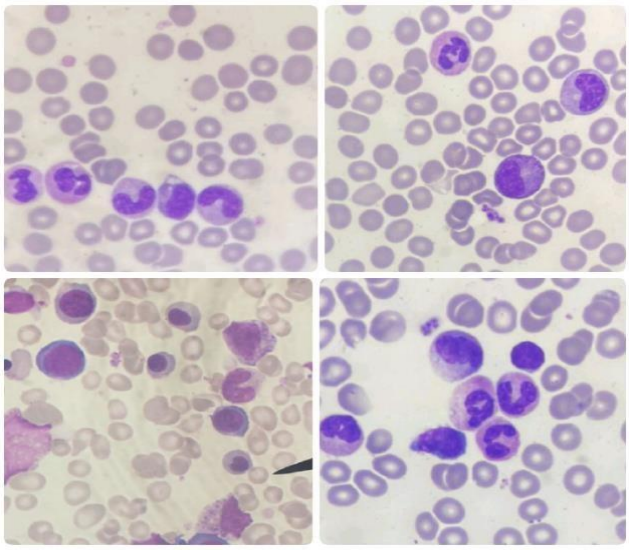

Figure 1.Blood smear showing the different signs of dysgranulopoiesis, stained with MGG and read with M.O. at the ×100 objective in the haematology department at the central laboratory of the CHU Hassan II of Fez.

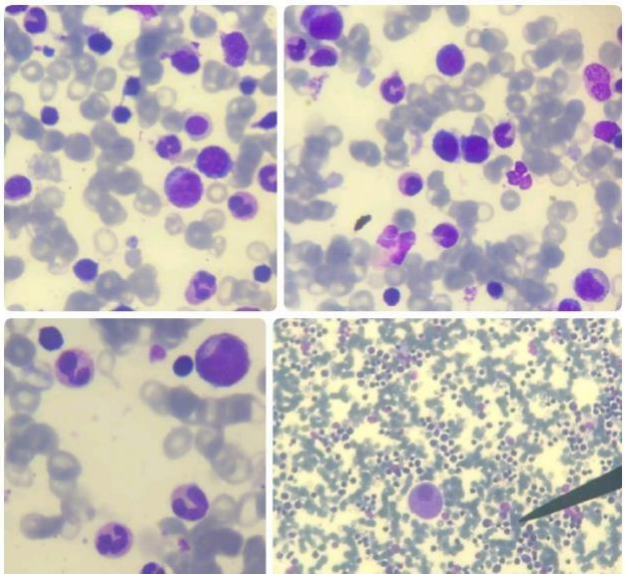

Figure 2: Medullary smear showing signs of dyserythropoiesis and dysmegakaryopoiesis.stained with MGG and read with M.O. at the objective ×100 in the haematology department at the central laboratory of the CHU Hassan II of Fez.

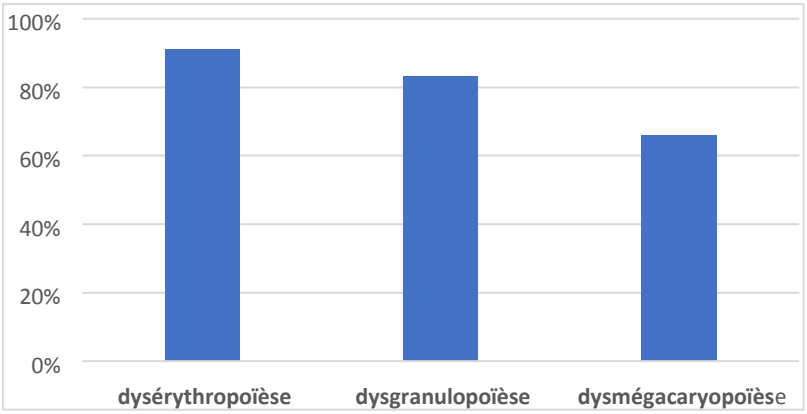

Figure 3.Morphological abnormalities present on the myelogram.

3. **Cytogenetic study:**
Karyotype was performed in 10 patients, 6 of whom had a normal karyotype, 3 in whom the karyotype was unsuccessful, and only one patient had an abnormal karyotype that objectified a 7q deletion.

WHO 2016 classification:
In our series and according to the WHO 2016 classification performed in 17 patients: an MDS with multilineage dysplasia (MDS - MLD) in 50%, no case had an MDS with unilineage dysplasia (MDS - SLD 1) or an MDS - RS with unilineage dysplasia (MDS - RS - SLD).On the other hand, 1 case had an MDS - RS with multilineage dysplasia (MDS - RS - MLD).
For MDS with Excess Blasts (MDS - EB), there were 3 cases of MDS - EB 1 and 1 case of MDS - EB 2. No case had MDS with isolated 5q deletion or unclassifiable MDS (MDS - U).

Course and complications:
In our series, 72% of our patients are always followed in the hematology department of the hospital, the clinico-biological surveillance and the regular follow-up of our patients allowed us to detect complications in 8 of our patients, it is about hemorrhagic complications represented by an epistaxis in 2 patients, a gingivorrhagia and rectorragia in another. Infectious complications represented by 2 cases of pulmonary infections. One case of transformation into acute myeloid leukemia was found, and hemochromatosis as a consequence of iterative transfusions in 2 patients.

IPSS prognostic classification:
In our study and according to the Revised International Prognostic Scoring system (IPSS-R), we found 10 patients at a low risk with a score between 2-3 ,7 patients have an intermediate risk with a score between 3.5-4.5 and only one patient at high risk with a score between 5-6.
Treatment:
Symptomatic treatment is based on transfusion of packed red blood cells, and platelet concentrates is administered in 60%, 30% of cases respectively, as well as 25% of transfused patients received iron chelators. And 33% of patients were put on EPO, and 30% on antibiotic therapy.

IV. Discussion:

According to our study, the average annual frequency of MDS is 6 cases per year (18 cases over 3 years). This is in line with the Algerian series of Guezlane et al. whose frequency is 7 cases per year [4]. On the other hand, this frequency remains lower than that reported by the national study of Yahyaoui et al. in Rabat whose frequency was 17 cases/year (155 cases out of 9) [5].

During our study, MDS was diagnosed in 18 patients, of whom 5 were men and 13 were women. There was a female predominance with a sex ratio of 0.38. Our results are similar to those reported by several series [4,6]. On the other hand, several studies show a clear male predominance [5, 7, 8, 9].

The mean age is 66 years with extremes ranging from 29 to 91 years. Our results are similar to those reported in several series: the series by Belakehal et al [10], where the mean age was 65 years, and the national series by Yahyaoui et al [5], where the mean age was 62 years. On the other hand, our patients are younger compared to those of several studies [11, 12, 13].

Only 5.6% of our patients have MDS secondary to cancer chemotherapy. This percentage is close to that reported in the study of Avgerinou et al. from Greece [14]. On the other hand, it is lower than that found in several studies, including the study by Neunkirchen et al. in Germany [15] and the study by Mukiibi et al. in

central Africa [16], while in the Spanish study by Iglesia et al. no cases of secondary MDS were diagnosed [17]. This difference could be explained by the relatively small number of patients recruited in our study.

The incidental discovery of an abnormal blood count (CBC) led to the diagnosis of 16.6% of MDS, whereas in the literature, incidental discovery is observed in 50% of cases. In our study, we found mainly an anemic syndrome, followed by a hemorrhagic syndrome and an infectious syndrome. Merlat noted this advantage of anemia which he found in more than 90% of cases [18]. Intragumtornchai T et al. found 84.6% of cases in their study in Thailand [14]. The comorbidities found in our patients are mainly chronic diseases frequently observed in geriatrics, namely diabetes, hypertension and cardiac diseases. These results are in agreement with the literature [15,18].

Anemia is the most frequent cytopenia in our series, present in 88.8% of patients, followed by thrombocytopenia in 55.5% and leukopenia in 38.8%. Isolated cytopenia was found in 50% of cases. Isolated anemia was found in 50% of cases, thrombocytopenia in 11%, and isolated white blood cell disease was very rare (5%). Bicytopenia is present in 22% of cases, and pancytopenia in 27%. Our results concerning the distribution of cytopenias are similar to those of several studies, in particular the study by Baiza et al. which found anemia in 96% of patients, thrombocytopenia in 44% and leukopenia in 35% of patients. Isolated cytopenia was found in 34% of patients, bicytopenia in 23%, and pancytopenia in 33% of cases [8].

The mean hemoglobin level of our patients was 8.6 with extremes ranging from 4.3 to 12.3. This level is higher than those found in several studies. The study by Nidaye et al. found 4.9 and Guezlane et al. 6.5g/dl [4,17]. According to our study, the anemia is normocytic (83%), followed by macrocytic (16%), and microcytic. This predominance of the normocytic type was found in the study by Bibi I, Hmissi B et al. who found it in 48% and 53% of cases respectively. On the other hand, Merlat et al. and Lowenthal et al. found a macrocytic predominance which is more frequent in the literature and which could be explained by the phenomenon of "ageing" of haematopoietic stem cells, marked by the loss of chromosomal telomeres causing accidents in the replication of nucleic deoxyribose acid (DNA) with a reduction in the number of mitoses of the medullary precursors, which thus give rise to mature cells of large size [18,20, 21,22].

Blood cytology has an orientation value, it allows to look for signs of dysplasia of the three lineages witnessing dyserythropoiesis, dysgranulopoiesis and dysmegacaryopoiesis. In our study we found signs of deserythropoiesis, dysgranulopoiesis and dysmegakaryopoiesis in 61%, 94% and 88% of patients respectively. This is consistent with the results of the literature [25].

Blast count is essential and must be done in a rigorous way. Indeed, it is one of the pillars of the WHO 2016 classification, it is also a major criterion of severity and finally, if it reaches 20% it indicates the evolution to acute myeloid leukemia. Therefore it is recommended to perform the count on 500 elements in order to be as accurate as possible [26].In our series only one case with a blast rate greater than 10% and no case of marrow blastosis greater than 20%.These results differ from that reported by : the study of Bernasconi et al . finds in 18.94% of cases a blast rate between 11 and 20% and a blast rate greater than 20% in 9.97% of cases. The series by Massimo et al. reports the presence of a blast rate between 11 and 20% in 12% of cases and a rate above 20% in 8% of cases [18, 19, 26].

The myelogram is important for the diagnosis of MDS; it provides two important parameters, namely the blast count and the existence of morphological abnormalities qualifying dysmyelopoiesis. The bone marrow of MDS is classically hyper- or normocellular, but may be hypoplastic in a minority of patients (about 10%). MDS are characterized by morphological abnormalities affecting one or more myeloid lineages as demonstrated on the myelogram. The existence of variable specificity of morphological abnormalities of the different myeloid lineages is an important point to take into account in the diagnosis of MDS, which corresponds to 10% of dysplasia of a hematopoietic lineage. Dysmegakaryopoiesis, as well as dysgranulopoiesis, have an important diagnostic value. In contrast, dyserythropoiesis is not very specific and has a low diagnostic value [27]. The classification of MDS is mainly based on the type of dysplasia and the percentage of marrow blasts. The percentage of bone marrow blasts may be increased in MDS but must remain strictly below 20%, which is the threshold for the diagnosis of AML.

The myelogram was performed in all patients and allowed the diagnosis to be made by specifying signs of dysplasia and the percentage of blasts. Dyserythropoiesis was found in 91% of cases, followed by dysgranulopoiesis in 83% of cases and dysmegakaryopoiesis in 38% of cases. Our results are similar to the study of Ehsan et al. and the study of Hmissi et al. which found dyserythropoiesis in 89% and 86% respectively [19,21].

Cytogenetic analysis of bone marrow should be performed for any suspected MDS to confirm the diagnosis. Karyotyping plays a major role in the identification of clonal chromosomal abnormalities, an essential criterion for establishing prognostic scores. New methods and recent technological advances allow for the detection of more and more mutations with greater accuracy. These chromosomal abnormalities are observed in 50 to 60% of cases. The most frequent are : - MDS associated with a deletion of the long arm of chromosome 5: del(5q), - monosomy of chromosome 7 or deletion of the long arm of chromosome 7: del(7q), 23 - monosomy of chromosome 8, - and a deletion of the long arm of chromosome 20: del(20q) (13). Some

clonal abnormalities are correlated with morphological and clinical abnormalities. MDS associated with del(5q) (5q- syndrome) are characterized by the presence of hypo or even mono-lobed megakaryocytes, refractory macrocytic anemia, normal or increased platelet count, and a favorable clinical course. MDS with pseudo-Pelger-Huët or vacuolated NPC abnormalities are associated with loss of the short arm of chromosome 17: del(17p). This abnormality has a poor prognosis and is more frequent in secondary MDS. When conventional cytogenetic analysis of bone marrow is not possible or has failed, fluorescence in situ hybridization (FISH) is of value in diagnostic and prognostic evaluation. This technique is useful for the clarification of complex aberrations and allows the detection of abnormalities in more than 15% of MDS patients with a normal karyotype.

The karyotype was performed in 10 patients, it came back normal in 60% of the patients .The karyotype of 3 patients failed, only one karyotype revealed a 7q deletion. During our study, 80% of patients had a favorable karyotype and 20% had an intermediate karyotype. These results are similar to those reported in the study by Greenberg et al. where the karyotype was favorable in 70% of cases and intermediate in 14%. The study by Matsuda et al. found a favorable karyotype in 77.5% of cases, intermediate in 14.7% of cases [18,19].

Determining the prognosis of MDS is a prerequisite for any therapeutic decision. Numerous prognostic scores for MDS have been reported in the literature. The Revised International Prognostic Scoring system (IPSS-R) is currently recommended and has been shown to provide a better prognostic assessment of overall survival and the risk of transformation to AML. This score is based on 3 criteria: the marrow blast count, the presence of specific cytogenetic abnormalities and the severity of cytopenias[27].

The main therapeutic issue for low-risk MDS is the correction of cytopenias and for high-risk MDS is the control of the leukemic clone. In our study, abstention was the therapeutic choice for 40% of the patients, transfusion was recommended in 60% of the patients (by packed red blood cells in 70% of the cases, by platelet concentrates in 30% of the cases), 33% of the patients were put on erythropoietin, and antibiotic therapy in 30% of these patients. Azacitidine (AHM) was used in 3 patients. Marrow transplantation remains the only curative treatment for MDS[27].

In the study by Kelaidi et al, 61% of patients received red blood cells and 61.7% received platelets. Azacitidine and decitabine were used in 18% of the patients in this American experiment. In the study by Ben Hassan et al, treatment was symptomatic in 57% of cases, with only one bone marrow allograft and one therapeutic abstention [23,28].

The regular follow-up of our patients allowed the detection of numerous complications such as: hemorrhagic complications in 16.6% of patients, infectious complications in 5% of patients, secondary hemochromatosis, consequence of iterative transfusions in 5% of patients and transformation into acute myeloid leukemia in 5.5% of patients. 10% of our patients died (nb=2), one of them by leukemic transformation. This rate is lower than that found in the study of Massimo et al. where the percentage of patients who died was 41%, 32% of whom died of leukemic transformation [19]. This can be explained by the number of patients in our study.

V. Conclusion:

Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis leading to cytopenias and bone marrow dysplasia, with eventual bone marrow blastosis and a marked probability of transformation into acute myeloblastic leukemia (AML) and Symptomatic treatment, based mainly on blood transfusions and prompt treatment of complications, remains fundamental in most MDS. However, to date, only hematopoietic stem cell allograft is potentially curative in MDS. These results are comparable to the data in the literature. However, the study sample and duration need to be extended. The use of new technologies such as flow cytometry (FMC) is a recent technology that has developed mainly over the last 15 years. It has proven its role in the diagnosis and follow-up of MDS.

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