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CHRONIC LYMPHOPROLIFERATIVE SYNDROMES: A STUDY OF 99 CASES

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ABSTRACT

Introduction: Chronic lymphoproliferative disorders (CLPD) are an heterogeneous group of diseases characterized by uncontroled production of lymphocytes that cause clonal lymphocytosis, lymphadenopathy, and bone marrow infiltration. **Methods:** A retrospective analysis (2014 to 2020) was carried out on the basis of 99 patients with lymphoproliferative disorders in the Laboratory of hematology of the Avicenne military hospital in Marrakech to describe the epidemiological, clinical, cytological characteristics of lymphoproliferative disorders. **Results:** Among 99 registered cases, there were 62 cases of multiple myeloma (MM) (62,62 %), 32 cases of chronic lymphoid leukemia (CLL) (32,3%), 3 cases of Sézary syndrome (SS) (3 %), a single case of Hairy Cells Leukemia (HCL) (1%) and a single case of prolymphocytic leukemia(LPB) (1%) were described. The median age of the patients was 61 (range: 41 to 80) years. There were 76 males (76%) and 23 females (24%), Male-to-female sex ratio was 3. Myelomas are the most frequently encountered in our series,bone pain is present in 78% of multiple myeloma patients, 6% have vertebral compression and 7% present chronic renal failure. Monoclonal gammopathy with kappa-type IgG is found in 60% of cases, IgG lambda in 26% of cases, IgA kappa in 5% of cases, IgM kappa in 4% of cases, and kappa light chains in 5% of cases.We found 32 cases of CLL, the average age is 65 years with extremes ranging from 45 to 78 years with a sex ratio of 5. Peripheral lymphadenopathy is the most frequent revealing symptom of the disease in 31 cases (50%) associated with splenomegaly in 2 cases, 45 % of cases were clinically asymptomatic. **Conclusions:** This retrospective study provides a clinical, epidemiological and cytological description of lymphoproliferative disorders in 101 cases

KEYWORDS: Lymphoproliferative syndromes - chronic lymphoid leukemia-multiple myeloma.

INTRODUCTION

Chronic lymphoproliferative disorders represent a relatively heterogeneous group of malignant blood diseases affecting mature cells of B and T lymphoid lineages.[1]

They should be classified according to the revised 2016 WHO classification. The diagnostic is based on a multidisciplinary approach taking into account clinical presentation, cytological, histopathological, immunophenotypical and cytogenetic.

There is a significant heterogeneity of clinical presentation and prognosis between the different chronic lymphoprliferative disorders, clinical evolution is characterized by relapses, cytological progression and transformation into diffuse large B cell lymphoma, aggressive lymphoma or high-grade lymphomas. These blood diseases each have specific clinical and biological features.

The objective of our work is determining the epidemiological aspects, the clinical signs of discovery and the various cytological characteristics of the chronic lymphoproliferative syndromes.

MATERIALS AND METHODS

It is a descriptive and analytic study of 99 patients with lymphocytosis confirmed by morphological examination, greater than or equal to 5 G / L, chronic (value stable for more than three months), between January 2014 and December 2020 in The laboratory of hematology of the Avicenne military hospital in Marrakech.

Inclusion criteria

The inclusion criteria consisted of a diagnosis of multiple myeloma, chronic lymphoid leukemia, Sezary syndrome, Hairy Cells Leukemia and prolymphocytic leukemia. Diagnosis is made by clinical orientation, hemogram result and the morphological study of cells on blood smears and myelogram, Electrophoresis of serum

proteins, Serum protein immune-fixation and radiological signs.

Exclusion criteria

Hyper lymphocytosis due to viral infections and chronic polyclonal hyperlymphocytosis were excluded from the present study.

RESULTS

Of the 99 registered cases, the median age of the patients is 61 years (41 to 80 years). There is 76 males (76%) and 23 females (24%) Male-to-female sex ratio is 3.

In this series, the prevalence of myeloma is 62, 6%, against 32,3% of chronic lymphocytic leukaemia , 3% of Sezary syndrome, and prolymphocytic and hairy cell leukemia are ranked last with 1% each (Figure 1).

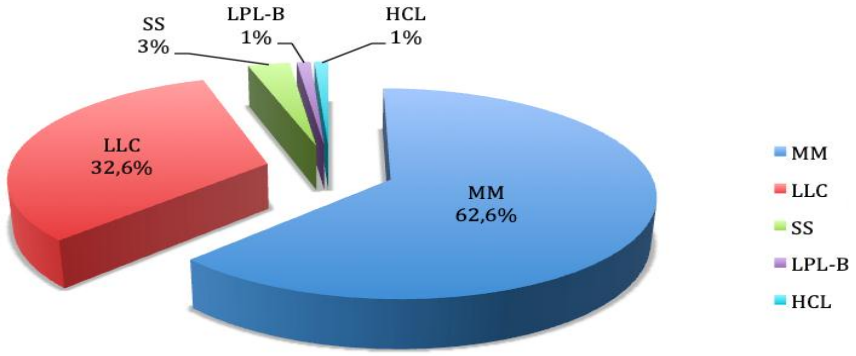

Figure 1: Distribution of chronic lymphoproliferative syndromes by type.

Myelomas are the most frequently encountered in our series. The average age is 55 with extremes of 41 to 80 years. The sex ratio is 2.5.

Among 62 myelomas, 78% have bone pain, 6% vertebral compression and 7% have chronic renal failure. The sedimentation rate is less than 30 mm at the first hour in 35% of patients, between 30 and 100 mm in 60% and very accelerated exceeding 100 mm in 5%. (Table I)

Table I: Clinical signs of Multiple Myeloma diagnosis.

Circumstances of discovery	Number of patients	Percentage
Bone pain	48	78 %
VS between 100 and 130 at 1st hour	3	5 %
Incidental discovery of a monoclonal peak in EPP	3	4 %
Vertebral settlement	4	6 %
Chronic Renal Insufficiency	4	7 %

Monoclonal gammopathy with kappa-type IgG is found in 60% of cases, IgG lambda in 26% of cases, IgA kappa in 5% of cases, IgM kappa in 4% of cases and kappa light chains in 5% of cases.

The diagnosis of myeloma is confirmed by the bone marrow smear, which showed between 10 and 98% of dystrophic plasma cells (central-core plasma cells, multinucleated cells, flamed cytoplasm, Mott cells). A rare case of association of myeloma with megaloblastosis is reported in this series.

After myeloma, chronic lymphocytic leukaemia comes in second place. The average age of patients is 65 years with extremes of 45 and 78 years. The sex ratio is 5.

Peripheral lymphadenopathy was the most frequent discovery, revealing the disease in 16 cases (50%). They were associated with splenomegaly in 2 cases (5%). the rest were clinically asymptomatic (45%) (Figure 2).

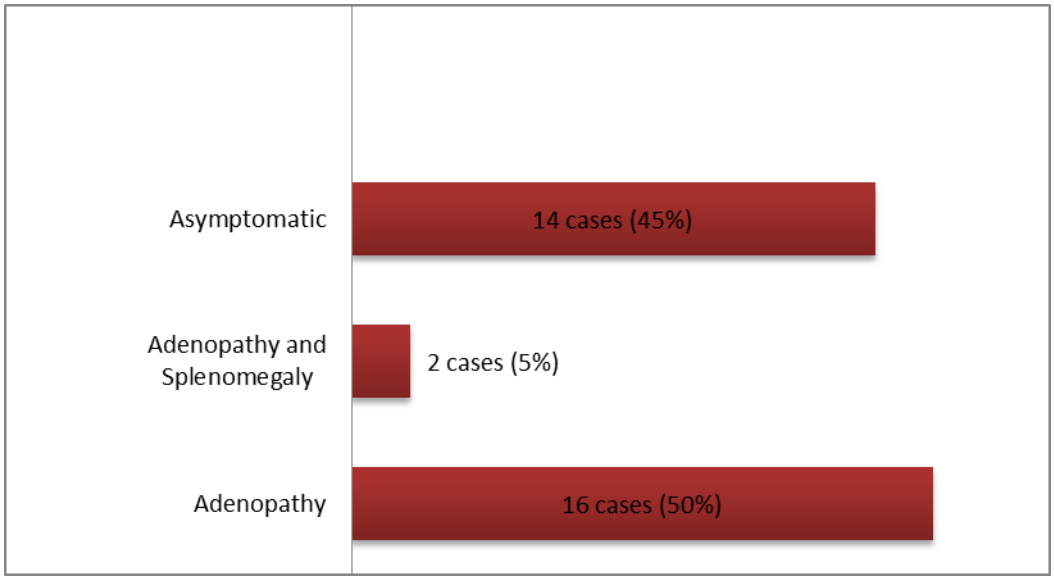

Figure 2: Circumstances of discovery of the LLC.

The diagnosis of CLL is made by a complete blood count that showed a hyperlymphocytosis of variable importance, always greater than 5G / l.

The other lines were also affected in 32 patients (91%), with a hemoglobin level varying between 8 and 11.5 g / dl in 19 cases (54,5%), a platelet count between 70 and 130 G / l in 1 case (3%), and an association between an anemia and thrombocytopenia in 12 cases (34,5%). (Table II)

Table II: Distribution of anemia and thrombocytopenia in patients with CLL.

Anemia and thrombocytopenia	Number of cases	Percentage
Isolated anemia	19	54,5 %
Anemia+Thrombocytopenia	12	34,5 %
Thrombocytopenia	1	3 %
No anemia or thrombocytopenia	3	9 %

The myelogram carried out in 8 patients, shows a lymphocyte infiltration of 30% to 91%, the other lines are quantitatively diminished. The lymphoid cells observed on blood smear and bone marrow smear had a small size with normal morphology , with a nucleus surrounded by a regular border of cytoplasm but little extended and weakly basophilic without granulations.

In our series, Sezary syndrome has a prevalence of 3% of total chronic lymphoproliferative syndromes. The skin lesions are the most frequent sign, 2 of the 3 patients present desquamating erythroderma with polyadenopathy, the other patient have parapsoriasiform lesions. Sezary cells represent 5 to 50% of the total lymphocytes, which corresponds to 0.5-35 G / L in absolute numbers these atypical lymphocytes are of variable size, mature, the nucleocytoplasmic ratio is high with a nucleus hyperconvolute or "cerebriform" characteristic and a scanty cytoplasm, discreetly basophilic and without granulationsof the cases recorded, 60% have normochromic normocytic anemia.

A single case of prolymphocytic leukemia B is reported, the patient presented a splenomegaly without peripheral lymphadenopathy, anemia, thrombocytopenia and hyperleukocytosis at 200 G / L. The lymphoid cells on the blood smear are large with a dense chromatin rounded nucleus and a prominent nucleolus. The percentage of these cells is 75%.

The prevalence of hairy cell leukemia is 1%. We reported a case of a patient with hepatosplenomegaly, a hemorrhagic syndrome due to deep thrombocytopenia at 40 G / L, an infectious syndrome and normochromic normocytic anemia. The successive haemograms of this patient showed pancytopenia with 3% of hairy cells, the bone marrow smear showed poor material with 5% of hairy cells. The diagnosis is based on the morphological identification of hairy cells, Flow Cytometry data showed a combination of the three markers CD11c, CD25 and CD103

DISCUSSION

Chronic lymphoproliferative syndromes(CLPD)represent a heterogeneous set of malignant hemopathies more frequently encountered in the elderly, with an incidence that increases with age.[2] The diagnosis requires a multidisciplinary approach including both clinical, histological, immunophenotypic and cytogenic aspects.[2]

There is a significant heterogeneity of clinical presentation and prognosis between the different (CLPD).

Multiple myeloma

According to the American Cancer Society, there are approximately 12,000 new cases of MM and about 9,000 MM-related deaths each year in the United States (10% of malignant hemopathy).[4] The diagnosis is based on the presence of ≥10% clonal bone marrow plasma cells or a biopsy proven plasmacytoma associated to one or more CRAB criteria (renal failure, hypercalcemia, lytic bone lesions and anemia). The main manifestations of myeloma result from the accumulation of malignant plasma cells in the bone marrow, which leads to the production and secretion of a monoclonal protein in the blood and/or urine, bone lesions, bone marrow failure with anemia and/or leukopenia and thrombocytopenia, immunosuppression with inhibition of normal immunoglobulin production and increased susceptibility to infection.

In this series, the prevalence of myeloma is 62,6%. This alteration of the general condition was often due to the delay in consultation and mainly concerned the elderly. Bone manifestations (pain, pathological fractures) frequently dominate the clinical picture.

The frequency of osteoarticular manifestations is variable from one series to another, but they are almost constant (65-90%). In our study, bone pain was the main revealing sign of the pathology (47 patients (78%), which concurs with the other series: Makni,[3] Bouataya and al.[4] Renal failure is found with a frequency of 7% in our series. Frequencies of (22% and 31%) were found in two large series of Blade and al,[5] and Hippe and al.[6]

For the 3 cases with a peak at electrophoresis, it is most often of type γ, regarding the isotypic distribution, the IgG type is predominant. The prominent place occupied by IgG in our series is also found in major international series where their proportion varies from 48 to 65%. In our series IgA ranks second with 5% of cases. This result is found in the Tunisian series of Mseddiet al.[7] and in the Spanish series of Giraldo et al.[8] where IgA accounts for more than 18% of cases.

While in most international series, IgM ranks second with more than 20 to 33% of monoclonal gammopathies. These differences may in part be explained by the higher prevalence of Waldenström disease in Western Europe compared to the Mediterranean basin. Other genetic and environmental factors that are not yet well known would be involved.[9]

The second particularity of our series is the frequency of light chain gammapathies which represent 5%. In international series, the frequency of this type of gammopathy varies from 2.7 to 14.13%, which shows the average prevalence of light chain myeloma in our hospital.[10]

The Salmon and Durie classification is the gold standard for prognostic evaluation. Stage III is the most frequent in most series (50 to 96.5%).[11,12] Our results are consistent with the data in the literature (82%).

Chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is the most common of the Chronic lymphoproliferative syndromes, it is considered as an indolent disease, common in adults and accounts for 12% of all hematological diseases,[13] 6% in Japan, 1.5% in Korea.[14] The crudeincidence rate per 100,000 individuals is 0.11in Korea.

Patients are initially asymptomatic and symptoms appear as the disease progresses, a third of patients will never need to be treated with a treatment, a third is symptomatic and requires treatment, the last third will be processed during the follow-up, it is recognized by its clinical but also prognostic heterogeneity. The etiologies are not well known.[15] CLL is defined by the presence and accumulation of small mature lymphocytosis in the bone marrow, blood and lymphoid organs, more than 5 G/L clonal cells, lasting more than three months, with monotypic proliferation. CLL cells are small lymphocytes with dense chromatin, a nucleus that virtually fills the cell with no nucleoli.[16] The diagnosis of CLL is confirmed by the study of lymphocyte membrane markers and a Matutes score greater than or equal to 4 when examined by immunophenotyping, a score strictly inferior to 3 points towards another lymphoproliferative B syndrome.[17] The median age at diagnosis ranges from 70 to 72 years.[18,19] The average age in our series is 55 years old withextremes ranging from 45 to 78 years which is in line with the results of international series, in the Young-Woo series the median age is 59 with extremes from 60 to 80 years old. In the Young-Woo series the median age is 59 with extremes from 60 to 80 years old.[17] Patients at diagnosis are often asymptomatic.[20] Two characteristics stand out in the study of our series, the sex ratio raised to 5 (1.5 to 2 in Europe) (1 to 1.4 in korea).[17] and the late discovery of the disease at the stage of ganglionic and splenic invasion in more than 90% of patients.[21]

Patients have a good performance status at diagnosis. Lymphadenopathy (cervical and axillary lymph nodes bilaterally and symetrical)may be observed in approximately 80% of cases, in our series, Peripheral lymphadenopathy was the most frequent discovery revealing disease in 31 cases (50%), They were associated with splenomegaly in 2 cases (5%). the rest were clinically asymptomatic (45%).

Anemia and thrombocytopenia are observed in 15-30% of patients with CLL.[22] In our case we foundan hemoglobin level varying between 8 and 11.5 g / dl in 19 cases (54,5%), and a platelet count between 70 and 130

G / l in 1 cases (3%). Some patients may also have a small serum monoclonal protein. Although in rare cases patients may not have lymphocytosis at diagnosis, peripheral blood and bone marrow are usually involved as the disease progresses.[22]

Although some CLL cases may have an atypical immunophenotype, the characteristic profile includes CD19/CD5/CD23/CD43/CD200 positivity with weak CD20 and CD11c positivity and dim surface immunoglobulin expression with restricted light chain expression.[22]

Sezary syndrome

Sezary syndrome comes third in our series. It is considered by authors as the leukemic variant of mycosis fungoides (MF), but it is classified separately according to the new WHO classification among cutaneous lymphomas,it is a cutaneous T-cell epidermotrophic lymphoma.[25] Men are more affected than women (incidence rate ratio: 1.6).[23] The incidence of this disease increases with age with the highest incidence at greater than 70 years of age.[24] Due to its rarity and requirement for careful clinicopathological correlation, diagnosis of Cutaneous T-cell lymphomas is frequently challenging and may be delayed. It may resemble benign inflammatory dermatoses, and the histological features of FM may be absent at the onset of the disease, even after several biopsies. Patient with Sezary syndrome typically present erythroderma, it is a diffuse erythemaaffecting 80% of the body surface area.[26,27]

In our series, Sézary syndrome has a prevalence of 3% of total diagnosed Chronic lymphoproliferative syndromes. There is a clear male predominance a result comparable to the data in the literature.[28] The average age of diagnosed cases is 47 years old, in the series of Zinzani et al the average age is between 55 and 60 years old.[29] With an apparent higher incidence in Africans and African-Americans.[30] According to Lutzner et al.[31] mycosis fungoides cells vary greatly in size. At times, they are small and indistinguishable from small lymphocytes.[31]

Hairy cell leukemia

Hairy cell leukemia (HCL) is recognized as an entity by the World Health Organization (WHO 2008).[32] And the 2016 revision of the WHO classification of lymphoid neoplasms.[33] HCL is more frequent in men than women, the splenomegaly present in 72% of cases is truly voluminous in only 18% of cases; moderate hepatomegaly is noted in 20% of cases; the signs of pancytopenia as initial symptoms are unequally distributed: the infectious manifestations are observed in 29 to 30% of cases, the anemic syndrome is noted in 27 to 28% of cases, hemorrhagic signs are indicative of the disease only in 4% of cases.[33]

CONCLUSION

Chronic lymphoproliferative disorders represent a relatively heterogeneous group of malignant blood diseases affecting mature cells of B and T lymphoid lineages.

The diagnosis is guided by the clinic, the data of the blood count and blood count formula. And the examination of blood smears as a first step, which will eventually be completed by Immunophenotyping of tumor cells, and histological study.

The management of Chronic lymphoproliferative disorders needs the collaboration between the hematologist and the biologist to assure an early diagnosis and a good prognosis.

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