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Chronic Lymphocytic Leukemia of *del* 17*p* in a Young Subject: About a Case and Reviewed a Literature

Amadou Djibrilla-Almoustapha[1,2*], Moustapha Mamane-Brah[3], Moustapha Elhadj-Chefou[4], Maman Rabiou Badé[1], Faiza Abba-Ousmane[1], Fanta Ousseini[1], Oumoulkairou Abdoulaye-Soumana[1], Badé Malam-Abdou[1,2]

[1]Departement of Onco-Hematology of the National Hospital of Niamey, Niamey, Niger
[2]Faculty of Health Science, Abdou Moumouni University of Niamey, Niamey, Niger
[3]Faculty of Health Science, André Salifou University of Zinder, Zinder, Niger
[4]Faculty of Health Science of Maradi, Maradi, Niger
Email: *amdjibrilla@gmail.com

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Abstract

Objective: To report a case of Chronic Lymphoid Leukemia in a 28-year-old young subject, with variable clinical features and a TP53 mutation, diagnosed and followed up in the Onco-Hematology department of the HNN. **Observation:** 28-year-old patient, having consulted for polyadenopathy and physical asthenia, whose clinical examination found a conscious patient, submaxillary, laterocervical, axillary and inguinal lymphadenopathy, bilateral, symmetrical, painless and non-compressive whose largest measures 3 cm in diameter. Hepato-splenomegaly and epistaxis. Predominantly lymphocyte hyperleukocytosis, immunophenotyping revealed low CD19+, CD5+, CD23+, CD20 monoclonal B lymphoid proliferation. The Matutes score was 4. A karyotype showed a three-chromosome translocation; the short arm of a chromosome 2, the long arm of a chromosome 11 and the long arm of a chromosome 13, and a translocation between the long arm of a chromosome 6 and the long arm of a chromosome 18. A FISH objectified a led 17p. The diagnosis of Binet Stage C CLL with positive *del* 17p and complex karyotype was retained. Despite the poor prognosis, the R-C (Rituximab-Chlorambucil) protocol was instituted with once-weekly transfusions. The patient is still alive in partial clinical and biological remission. **Conclusion:** Despite therapeutic progress, the presence of the deletion of chromosome 17p with TP53 mutation and the young age of the patient does not change the patient's prognosis.

Keywords

Chronic Lymphocytic Leukemia, Young Subject, *del* 17 p, HNN, Niger

1. Introduction

Chronic lymphocytic leukemia (CLL) is a malignant haemopathy characterized by a monoclonal proliferation of mature lymphocytes with normal morphology and phenotype B, responsible for bone marrow, blood and/or lymph node infiltration [1]. It represents 1% of cancers and 12% of hematological malignancies in Europe. Milena Sant and *al* for the Haemacare group (48 European registries from 20 different countries) did not show any variation in CLL incidence across Europe. The average age at the time of diagnosis is 70 years in men and 72 years in women. It is very rare before the age of 40, and never described before the age of 10 [1]. In Senegal and Niger, the average age of diagnosis was 59 and 61 years, respectively [2] [3]. It is a slowly evolving pathology with multiple infectious, hemolytic and autoimmune complications [1]. Nowadays, the prognosis is established by the search for the *del* 17p and the TP53 mutation which is of great contribution to the modification of the therapeutic attitude. Despite the many advances in this pathology, progress remains to be made in the therapeutic field. We report a case of Chronic Lymphoid Leukemia in a young 28-year-old subject, with variable clinical features and a TP53 mutation, diagnosed and followed up in the Onco-Hematology department of the HNN.

2. Observation

This was a 28-year-old patient, married and father of a child, the first of 8 siblings (3 boys and 5 girls), with a surgical history of right knee arthroscopy. He has consulted for polyadenopathy and physical asthenia. The clinical examination found a conscious patient with a good general condition (WHO2), intense mucocutaneous pallor, Weight: 89 kg, Height 1.98 meters, body surface area (SC): 2 m^2, Blood Pressure (AP) 120/60mmHg, Temperature (T˚) at 37˚C is 97% SPO2. A tumor syndrome consists of submaxillary, laterocervical, axillary and inguinal lymphadenopathy, bilateral, symmetrical, painless and non-compressive, the largest of which measures 3 cm in diameter. Painless splenomegaly with splenic overflow at 22 cm, hepatic arrow hepatomegaly at 18 cm. A hemorrhagic syndrome is made up of bilateral epistaxis and alternating diarrhea and constipation. A Complete Blood Count (CBC) showed hyperleukocytosis (GB: 129,000/mm^3) with lymphocyte predominance (23,458/mm^3), anemia (Hb: 4 g/dL) normochromic (MCHC: 32%) normocytic (VGM: 99 fl) non-regenerative (Reticulocytes: 45,800/ml) and thrombocytopenia (Plt: 42,000/mm^3). Depending on the lymph node areas affected and the CBC, the patient is classified as Binet stage C. The blood smear was rich in cells. There was a large mature lymphocyte population at 90%, small size, high N/C ratio, basophilic cytoplasm of mottled chromatin

Immunophenotyping revealed low CD19+, CD5+, CD23+, CD20 monoclonal B lymphoid proliferation. The Matutes score was 4 in favor of SLPB type LLC. The hematological karyotype showed in fifteen mitoses out of twenty, a three-chromosome translocation; the short arm of a chromosome 2, the long arm of a chromosome 11 and the long arm of a chromosome 13, nine out of fifteen mi-

toses present in addition a translocation between the long arm of a chromosome 6 and the long arm of a chromosome 18. A FISH was carried out which objectified the *del* 17p. Based on clinical data, complete blood count, immunophenotyping, hematological karyotype and FISH, the diagnosis of Chronic Lymphoid Leukemia (CLL), Binet Stage C with positive *del* 17p and complex karyotype was retained (Table 1). The rest of the assessment showed the C Reactive Protein (CRP) at 0.3 ng/l, a Sedimentation Rate (ES): 170 mm/1st hour, an RAI which was negative, an LDH level at 248.76 UI/l, a young blood glucose level of 3.60 mmol/l, an azotemia of 3.19 mmol/l, a creatinine level of 61 µmol/l, an albumin level: 35.5 g/l, a thick drop: positive, fibrinemia at 7.41 g/l, serum calcium at 85 mg/l, uric acid level at 63 mg/l, haptoglobin at 2.84 g/l, total bilirubin at 5 mg/l, blood group rhesus A negative. The cervical-thoracic-abdominal and pelvic CT scan (CTAP) had objectified hepatosplenomegaly with cervical, mediastinal, abdominopelvic and bilateral inguinal polyadenopathies as well as pulmonary parenchymal involvement. After a multidisciplinary discussion, despite the poor prognosis, the patient was put on an R-C protocol (Rituximab- Chlorambucil) with transfusions once a week.

3. Discussion

Chronic Lymphoid Leukemia (CLL) is a lymphoid hemopathy of the elderly; it represents 1% of cancers and 12% of malignant hemopathies in Europe. The average age at diagnosis is 70 years in men and 72 years in women. It is very rare

Table 1. Biological diagnostic data.

Biology report	Units	Values
Complete Blood Count (CBC)	leukocytes/mm^3	129,000
	Lymphocytes/mm^3	23,458
	Hemoglobin (g/dL)	4
	Platelets/mm^3	42,000
Immunophenotyping	CD19	+
	CD5	+
	CD23	+
	CD20.	+
	Matutes	4
Karyotype	Chromosome 2	Short arm translocation
	Chromosome 11	Long arm translocation
	Chromosome 13	Long arm translocation
	Chromosome 6	Long arm translocation
	Chromosome 18	Long arm translocation
FISH	17p	deletion

before the age of 40, and never described before the age of 10 [1]. Our patient was 28 years old at the time of diagnosis, which is rarely described in the literature. This rarity of age is due to a probable decrease in the self-renewal of hematopoietic stem cells encountered in the elderly, as well as an alteration of their differentiation programs but also due to immunosenescence which is a progressive alteration. of the immune system in general linked to age as well as a reduction in the renewal of hematopoietic cells linked to intrinsic, extrinsic and hormonal factors in particular [2].

The clinical manifestations are most often dominated by a tumor syndrome marked by polyadenopathies generally located in the cervical and supraclavicular, axillary, and inguinal areas, often painless, firm, bilateral and symmetrical, as well as hepato-splenomegaly, or even signs bone marrow failure at an advanced stage of the disease [3] [4]. The importance of this tumor syndrome makes it possible to identify the evolutionary stage according to the Binet classification in three different stages including stage A (65%): absence or presence of a lymph node area without anemia or thrombocytopenia; stage B (28%): the presence of at least three lymph node areas, without anemia or thrombocytopenia and stage C (9% of cases): the presence of anemia (hemoglobin less than 10 g/dl) or thrombocytopenia (platelets less than 100×10^9/l), regardless of the number of lymph node areas [5]. Our patient is classified as Binet stage C.

The diagnosis of CLL is based on recently modified criteria: they associate the presence of small mature lymphoid cells, with mottled chromatin on the blood smear and blood B lymphocytosis greater than 5×10^9 /l persisting for more than 3 months [6]. The FAB classification identifies several variants but the most typical are small lymphoid cells, with a nucleus surrounded by a ring of cytoplasm, but not very extended to the FS, a major lymphocytosis greater than 6×10^9/l [7]. This is the case of our patient with lymphocytosis at 23,458/mm^3.

The study of membrane markers (flow cytometry) is essential to confirm the diagnosis of CLL. Leukemia cells carry the characteristic antigens of the B lineage, in particular, the pan-B marker CD19 and the marker CD20 for mature B cells.

The Royal Marsden Hospital (RMH) score, also known as the Matutes score, gives a value of 1 to positive CD23 and CD5, negative or low expression of FMC7 and CD79b. These immunological characteristics make it possible to establish the Matutes score which should be greater than or equal to 4, indicating the typical character of CLL or atypical if the score is equal to 3, if it is less than 3 the diagnosis of CLL must be challenged. In our patient, despite his young age, immunophenotyping noted low monoclonal B lymphoid proliferation CD19+, CD5+, CD23+, CD20 with a Matute's score of 4 comparable to those of elderly subjects.

The karyotype has been replaced in favor of the technique of fluorescent in situ hybridization (FISH) on interphase cell nuclei, which makes it possible to find clonal genomic aberrations (FISH) in approximately 80% of affected patients. The discovery of these abnormalities has made it possible to understand

the pathogenesis of the disease because they are located at the level of candidate genes: 17p 13 (TP53) 11 q22-q23 (ATM) [8].

We found in the karyotype of our patient, in fifteen out of twenty mitoses, a three-chromosome translocation; the short arm of a chromosome 2, the long arm of a chromosome 11 and the long arm of a chromosome 13, nine out of fifteen mitoses present in addition a translocation between the long arm of a chromosome 6, and the long arm of a chromosome 18. FISH revealed a *del* 17p with TP53 mutation. Hence the complex karyotype in our patient.

The TP53 gene is located on the short arm of chromosome 17 in position 17p13.1 and germline mutations of TP53 predispose to the occurrence of multiple cancers at an early age generally associated with a poor prognosis [9].

In 77% of cases the *del* 17p was detected before treatment and 23% of cases after; and 55 cases of TP53 mutations [9]. In the majority of cases, the deletion resulted from an unbalanced translocation with another partner (70%). The karyotype was in favor of a translocation between chromosomes 2, 4 and 11 resulting in a loss of 11q and a gain of 2p [2]. Eight percent (8%) of patients had *del* 17p, corresponding to the inactivation of the P53 gene and conferring resistance to chemotherapy. Its frequency increases with the progression of the disease: 7% of *del* 17p at stage A versus 35% at stage C [10].

The prognosis of CLL has long been considered unpredictable. Rai in 1975 published a five-stage prognostic classification that remained widely used and was recently modified in 1981 for which Binet proposed a three-stage classification (A, B, C) widely used today. These two classifications are very limited. Lymphocyte doubling time < 12 months, elevated serum beta-2-microglobulin, B cell CD38 positive, elevated serum thymidine kinase, unmutated IgVH mutation status, positive ZAP-70 were unfavorable prognostic factors [10] [11].

The prognostic impact of new factors related to CLL biology has been evaluated over the past 15 years. Several studies have demonstrated the influence of the date of onset of *del*17p on overall survival. In fact, if detected de novo at the time of diagnosis, overall survival is 4 to 5 years. On the other hand, it drops to 12 or even 18 months if the anomaly was identified during follow-up, as an additional anomaly. Moreover, some studies have shown that progression-free survival and overall survival of 17p- patients are inversely proportional to the size of the 17p-clone [2] [9] [10].

The diagnosis of our patient was that of Chronic Lymphoid Leukemia (CLL) at Binet Stage C with positive *del* 17p in the complex hematological karyotype.

Once the patient is deemed eligible for treatment, the choice of protocol is based on an assessment of the risk/benefit balance: benefit in progression-free survival and/or overall survival, quality of life, toxicity and treatment constraints.

Few substances are effective in patients with P53 pathway abnormalities. In the first line, the percentage of patients with a P53 anomaly represents less than 10% and is estimated between 5% and 7% depending on the trials. Fludarabine, alkylating agents and Rituximab are not very effective with rare complete and short remissions. Other substances seem to have some efficacy such as lenalido-

mide, Bruton Tyrosine Kinase (BTK) inhibitors for patients with *del* 17p, treatment is currently based on a combination of alemtuzumab and high-dose corticosteroids [12].

4. Conclusion

Chronic Lymphoid Leukemia (CLL) is a mature lymphoid hemopathy in the elderly, very rare before the age of 40, and never described before the age of 10. Despite therapeutic progress, the presence of chromosome 17p with TP53 mutation and the young age of the patient does not change the patient's prognosis. Treatment is currently based on immunotherapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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