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CD5-Negative Chronic Lymphocytic Leukemia: a Report of Three Cases

La leucémie lymphoïde chronique CD5 - négative : à propos de trois cas

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative syndrome characterized by the progressive accumulation of small B-line lymphocytes [1]. These B lymphocytes (LB) are marked by CD5+ yet a marker of T lymphocytes (LT), CLL is also a dysimmune disease characterized by autoimmune phenomena which manifests as autoimmune cytopenia [2]. The CD5 molecule definitely intervenes in signal transduction by exerting a negative retrocontrol on the BCR and the TCR via signaling factors in almost 100% of these cells. CD5 therefore induces the survival [3] of B cells through the production of IL-10 and exerts negative feedback on BCR signaling [4]. Since this marker is intimately linked to the pathogenesis and clinical manifestations, we report three cases of chronic lymphocytic leukemia (CLL) with CD5 negative in elderly black Africans at the clinical hematology department of Abidjan CHU in Yopougon. Our patients were over 50 years old and presented with a tumor syndrome (adenopathy and/or splenomegaly) + lymphocytosis >5000 with small mature lymphocytes and the phenotypic markers of the Matutes score. The patients were classified Binet C and one had the positive Coombs test. The cytogenetic study was not carried out to see chromosomal abnormalities. Treatment was based on immunochemotherapy with protocols (R-CD; R-CHOP; R-Cloraminofen). The evolution of the disease will be evaluated mid-term and at the end of the treatment to assess the therapeutic response. The less common CD5 negative CLL presents almost the same clinical, biological and therapeutic characteristics as the other forms of CLL. The cytogenetic and biomolecular study should be carried out to see the chromosomal abnormalities and the mutational profile.

RÉSUMÉ

La leucémie lymphoïde chronique (LLC) est un syndrome lymphoprolifératif caractérisé par l'accumulation progressive de petits lymphocytes de lignée B. Bien que ces lymphocytes B (LB) soient marqués CD5+, un marqueur des lymphocytes T (LT), la LLC est également une maladie dysimmunitaire caractérisée par des phénomènes auto-immuns se manifestant sous la forme de cytopénies auto-immunes. La molécule CD5 intervient de manière déterminante dans la transduction des signaux en exerçant un rétrocontrôle négatif sur le BCR et le TCR via des facteurs de signalisation dans presque 100 % de ces cellules. Ainsi, le CD5 induit la survie des cellules B par la production d'IL-10 et exerce une rétroaction négative sur la signalisation du BCR. Étant donné que ce marqueur est intimement lié à la pathogenèse et aux manifestations cliniques, nous rapportons trois cas de leucémie lymphoïde chronique (LLC) avec CD5 négatif chez des Africains noirs adultes au service d'hématologie clinique du CHU d'Abidjan à Yopougon. Nos patients avaient plus de 50 ans et présentaient un syndrome tumoral (adénopathie et/ou splénomégalie) + lymphocytose >5000 avec des petits lymphocytes matures et des marqueurs phénotypiques du score de Matutes. Les patients ont été classés Binet C et l'un d'entre eux avait un test de Coombs positif. L'étude cytogénétique n'a pas été réalisée pour identifier les anomalies chromosomiques. Le traitement était basé sur l'immuno-chimiothérapie avec des protocoles (R-CD ; R-CHOP ; R-Cloraminofen). L'évolution de la maladie sera évaluée à moyen terme et à la fin du traitement pour évaluer la réponse thérapeutique. La forme moins courante de LLC à CD5 négatif présente presque les mêmes caractéristiques cliniques, biologiques et thérapeutiques que les autres formes de LLC. L'étude cytogénétique et biomoléculaire devrait être réalisée pour identifier les anomalies chromosomiques et le profil mutationnel.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a chronic hemopathy characterized by the accumulation of small mature lymphocytes blocked in the G0 phase of the cell cycle. This accumulation is secondary to a defect in apoptosis involving numerous pro- and anti-apoptotic factors. In CLL, there is hyper-expression of anti-apoptotic markers and, on the contrary, a lack of expression of pro-apoptotic molecules. [1]. CD5 is definitely involved in signal transduction by exerting a negative feedback control on the BCR and TCR via signaling factors, and its role has been proven in maintaining CLL cells in anergic state in vivo and in their proliferation with inhibition of programmed cell death via mechanisms which are not yet fully elucidated, but which involve molecules such as IL-10 or calcium [5]. This heterogeneity is linked to the characteristics of the tumor cell and the different responses to apoptosis signals depending on the expression of molecules, in particular CD5, on their surface. CLL is the most common leukemia in adults, accounting for 12% of all hemopathies [6]. The diagnosis is made in the presence of lymphocytosis greater than 5000G/L for more than three months, associated with phenotypic markers with a Matutes score ≥ 4. CD5 positive in almost 100% of cases [3]. CD5 negativity is a rare occurrence in CLL, which is why we present these three (3) cases.

PRESENTATIONS OF THE CASES

Patient 1

Patient K M, aged 71, housewife with no major history, resident in Abidjan. Received in August 2021 for investigation of hyperleukocytosis with lymphocyte predominance plus anemia (Hb= 6.7 g/dl; lymphocytes = 13,000 /mm3).

The clinical picture had been evolving for 03 months, marked by the discovery of a blood lymphocytosis of 12,700 during a routine check-up. In view of the persistence of the lymphocytosis after ATB-based treatment, she was referred to our department for treatment.

Clinical examination on admission revealed the following: T°= 37.8°C, BP=120/70 mmHg, P=58 Kg average general condition (WHO1) pale conjunctivae with no jaundice or IMO. Bilateral painless firm mobile axillary audiopathies, 1-1.5 cm in diameter with Hackett type II splenomegaly were noted. The hemogram showed a hyperleukocytosis GB= 19,000/mm3 with lymphocyte predominance 13,000/mm3, an anemia of 6.2 g/dl, platelets were normal; the blood smear found lymphocytosis with 88% mature lymphocytes. Neutrophils 10%, monocytes 2%, lymphocyte immunophenotyping on peripheral blood concluded: CD19+, CD5-, CD23+, CD43+, FMC7-, CD79b -, CD20+, CD30- low expression of kappa light chain. Matutes is 4. The diagnosis of chronic lymphocytic leukemia was made. In the extension workup, CT scan found supra-centimetric bilateral axillary adenopathy, CD30-, LDH= 218UI/L, ferritin = 755.79 ng/l, albumin = 34 g/L with a positive direct Coombs test. The patient was classified as immunologically BINET C. Cytogenetic analysis to look for pejorative chromosomal abnormalities was not performed. The diagnosis of BINET C chronic lymphocytic leukemia with autoimmune cytopenia was accepted and treated with protocol R CD 6cures.

Patient 2

Patient B K G, aged 50, housewife with no major history. She was received in September 2021 for splenomegaly and abdominal polyadenopathy evolving for 2 years, marked by the appearance of a mass in the left hypochondrium, progressively increasing in size, associated with nocturnal hyper sudation, subjective weight loss and intermittent fever without focus. This prompted herbal therapy. The course was marked by persistence and worsening of the signs and the onset of abdominal pain associated with constipation. She decided to consult her doctor and underwent an abdomen-pelvic CT scan, which was referred to us for further management.

The clinical examination on admission was as follows: T°= 37°C, BP=12/7 cm/Hg, P=58 Kg, average general condition (WHO 1), pale conjunctivae without jaundice or OMI, Hackett's Splenomegaly type IV. The blood count showed a hyperleukocytosis WBC= 96580/mm3 with lymphocytes at 89040/mm3, 85% of which were small mature lymphocytes, with a thin cytoplasm. The nucleus was regular, the nucleoli were not or only slightly visible and the cytoplasm was homogeneous and devoid of granulations. The other findings were: anemia at 5.2 g/dl, thrombocytopenia at 64,000 /mm3. Lymphocyte immunophenotyping showed CD19+, CD5-, CD23+, CD43+, FMC7+, CD79b-, CD20+, CD30-. Concerning prognosis, CT showed abdominal polyadenopathies and splenomegaly. Other serum testes showed: LDH= 218I U/L, albumin = 30 g/L with a negative direct Coombs test. The patient was classified according to the BINET C classification. Cytogenetic analysis for pejorative chromosomal abnormalities was not performed. The diagnosis of BINET C chronic lymphocytic leukemia was accepted.

Patient 3

Patient Y A, aged 69, bricklayer with no previous history, was living in Abobo. He was received in October 2021 for polyadenopathies evolving for 09 months, marked by the appearance of a cervical mass, progressively increasing in size, associated with nocturnal hyper sudation, subjective emaciation and intermittent fever without infectious focus. This prompted herbal therapy. The evolution was marked by the persistence and aggravation of the signs and the appearance of other axillary and inguinal masses associated with intense physical asthenia and dizziness. The patient decided to consult a center from which he was referred to our department. Clinical examination on admission was as follows / T°= 37.8°C, TA=120/70 mmHg, P=58 kg, average general condition (WHO 2), slightly discolored conjunctiva without jaundice or OMI, cervical, axillary and inguinal bilateral mobile painless asymmetric non inflammatory ADP 2-4 cm in diameter without palpable splenomegaly. The hemogram showed

hyperleukocytosis WBC= 126 000/mm3 predominantly lymphocytes 98 650/mm3, with mature lymphocytes at 83%, neutrophils at 12%; monocytes at 1%; eosinophils at 4%. Lymphocyte immunophenotyping showed CD19+, CD5-, CD23+, CD43+, FMC7-, CD79b -, CD20+, CD30-low kappa light chain expression.
The extension workup was as follows: the chest X-ray was normal and the abdominopelvic ultrasound showed mesenteric and ileocecal abdominal adenopathies with a normal-sized micro nodular liver without splenomegaly. LDH = 419I U/L, uric acid 70 mg/L, albumin = 30 g/L, CD30. The patient was classified according to the BINET C classification. Cytogenetic analysis for pejorative chromosomal abnormalities was not performed, and the immunological work-up showed a negative direct Coombs test. The diagnosis of chronic lymphocytic leukemia classified as BINET stage C was accepted.

DISCUSSION

Given that CLL is the most common leukemia in adults and represents 12% of all hemopathies [6], the diagnosis is made in the presence of lymphocytosis greater than 5000G/L evolving for more than three months associated with phenotypic markers with a Matutes score ≥ 4. CD5 positive in almost 100% of cases [3]. We report three cases of CD5-negative CLL, which is exceptional. CD5 is definitely involved in signal transduction by exerting a negative feedback control on the BCR and TCR via signaling factors, and its role has been proven in maintaining CLL cells in anergy in vivo and in their proliferation with inhibition of programmed cell death via mechanisms that are not yet fully elucidated but which involve molecules such as IL-10 or calcium [5]. This heterogeneity is linked to the characteristics of the tumor cell and the different responses to apoptosis signals depending on the expression of molecules, in particular CD5, on their surface. In South Saharan Africa, and more specifically in the Ivory Coast, our observations require some comment from the clinical, biological, and evolutionary points of view. This observation suggests that this form of CLL is rare in Côte d'Ivoire. This assertion calls for some reservations, given that patients are only received late in the hematology department and immunophenotyping, which should confirm the diagnosis, is not carried out on site and is not financially accessible for most patients. CD5 is a hallmark of CLL cells, being present in almost 100% of them [3]. It also plays a definite role in signal transduction, exerting negative feedback on the BCR and TCR via signaling factors [4]. In accordance with the literature [6], our patients were aged over 50 years. Clinically, the patients had a tumor syndrome, which is consistent with the data of E Padaro et al in Togo [7] who reported a frequency of 81%, but we note that the tumor syndrome is much more marked if the duration of evolution is longer. Splenomegaly is present in most cases [7], but we noted the absence of splenomegaly in one patient, which is rare in CLL. The hemograms of our patients showed respectively: hyperleukocytosis with lymphocyte predominance, anemia; the blood smear found lymphocytosis with mature lymphocytes. In all three cases, we found blood lymphocytosis (lymphocytes greater than 5000/mm3) with variable values, which is consistent with data in the literature. All three diagnoses were made by immunophenotyping of peripheral blood, which revealed these different markers, with specificity for CD5 negativity, which is rare in CLL. In terms of prognosis, two of our patients had more than three lymph node areas with 2 to 3 signs of biological progression and CD30-, K M, had a positive Coombs test. The patients were all classified as Binet C. The lymphocytosis duplication time was not assessed as we received patients at an advanced stage of the disease. Cytogenetic tests for chromosomal abnormalities and molecular biology tests for mutational profiles were not carried out due to a lack of financial resources, which could have had an impact on management and possibly show us whether the negative CD5 was linked to a chromosomal abnormality or a specific mutational profile. From a therapeutic point of view, patients are treated according to protocols based on the molecules available and the patient's socio-economic circumstances. The therapeutic response will be assessed after 03 months of the last course of chemotherapy, which will include a clinical and biological evaluation using criteria defined according to the data in the literature.

CONCLUSION

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults, accounting for 12% of all hemopathies. CD5 negativity is a rare finding in CLL and it would be important to analyze CD5, cytogenetic abnormalities and mutational profiles to improve understanding of the management of this form of CLL.