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A Rare Entity of Accelerated Chronic Lymphocytic Leukemia: A Report of Two Cases and Review of Literature

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Abstract

Background: Accelerated-chronic lymphocytic leukemia (A-CLL) is a rare disease entity as it represents less than 1% of all reported cases of chronic lymphoid leukemia (CLL). Moreover, it is most likely an under diagnosed entity due to its rarity and the non-standardized practice of lymph node biopsy in CLL. **Purpose:** The aims of our work are to establish the diagnosis of A-CLL and to study the prognosis and treatment of this rare entity. **Method:** here, we report the clinical presentation and the follow up of two cases of A-CLL. **Results:** Distinguishing Richter transformation (RT) from A-CLL is important as it may result in a major change in disease management. The prognosis of A-CLL is intermediate between CLL and RT. The prognosis is mainly poor due to a predominance of poor prognostic markers including an increasing number of p53-positive cases. **Conclusion:** To this date, no prospective study has been led to define the best treatment for A-CLL. The shorter survival of A-CLL when compared to typical CLL implies the need of a more aggressive treatment.

Keywords

Accelerated Chronic Lymphocytic Leukemia, Richter Transformation, Prognosis, Treatment

1. Introduction

Chronic lymphocytic leukemia (CLL) is a common type of leukemia representing 25% to 30% of cancers in western countries [1]. The transformation to an ag-

gressive lymphoma, as a diffuse large B-cell lymphoma, known as Richter transformation (RT), occurs in 10% of cases [2] [3]. The accelerated CLL (A-CLL) is a rare entity first described by Pugh and colleagues in 1988 [4]. It is a rare histological variant of CLL with a frequency of less than 1% of all CLL cases. It has an aggressive clinical presentation and is often mistaken with Richter's syndrome [5]. It is characterized by the increase of proliferation centers in size and the elevation of proliferation indices in the lymph node. Due to the rarity of this form, the optimal management is still not established. Distinguishing RT from A-CLL is important for the management. In this study, we report the clinical presentation and the follow up of two cases of A-CLL.

2. Cases

2.1. Case n˚1

A 48-year-old male with no past medical history, was diagnosed in May 2012 with lymphocytic lymphoma B. The patient reported one year symptoms evolution including fatigue, anorexia, progressive weight loss and night sweats with progressively increasing cervical lymphadenopathy. Physical examination revealed a 6 cm sized bilateral cervical lymphadenopathy and a 3cm sized bilateral supra-clavicular lymphadenopathy. CBC showed white blood cell count 9200/mm^3, 70% granulocytes, 21% lymphocytes, 6, 4% monocytes, hemoglobin 14.8 g/dl and platelets 176,000/mm^3. He had high levels of lactate dehydrogenase at 754 UI/l (reference range ≤ 270 U/L). The computed tomography scan showed multiple lymphadenopathies above and below the diaphragm. The histologic funding of the cervical lymph node biopsy showed diffuse lymphoid proliferation formed by small lymphocytes. Immunohistochemically, the tumor cells were positive for CD20, CD79a, CD23 and lowly positive for CD5 and negative for CD10 and cyclin D1. Bone marrow biopsy showed infiltration by a small cell B lymphoma. Due to the presence of B symptoms, the patient received immunochemotherapy type RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) with complete remission after 6 courses. In September 2015, reappearance of B symptoms with bilateral cervical and axillary lymph nodes of 2 to 3 cm long axis. CBC showed white blood cell count 11,900/mm^3, 58% granulocytes, 31% lymphocytes, 9% monocytes, hemoglobin 12.4 g/dl and platelets 137,000/mm^3. A Positron Emission Tomography (PET) was not performed at that time, but the cervical lymph node biopsy concluded to a CD20+ diffuse large B cell lymphoma (RT). The bone marrow biopsy concluded also to RT. The New Generation Sequencing (NGS) testing was not available to determine the clonal origin. The re-examination of the initial biopsy showed a lymphoid proliferation with cells type pro-lymphocyte and para-immunoblasts with growth nodules and a high Ki67 index >40% concluding to an A-CLL (**Figure 1**).

The patient received FCR protocol (Fludabine, Cyclophosphamide, and Rituximab) complicated by a septic shock causing his death after the third course.

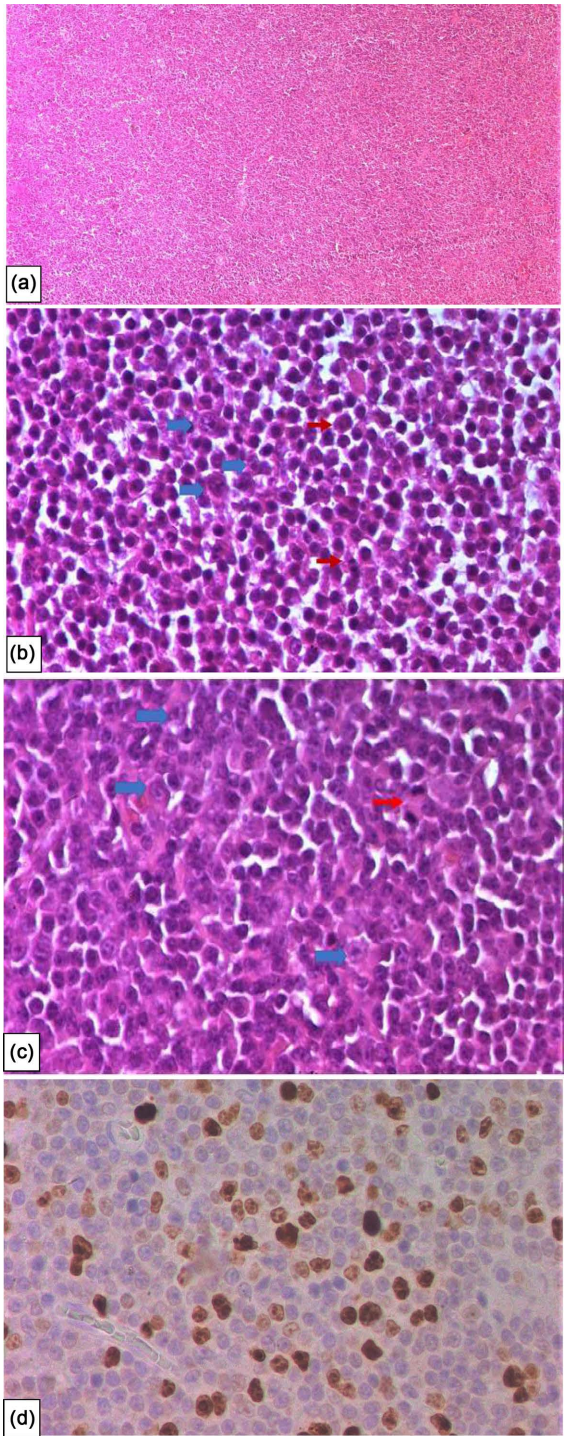

Figure 1. The re-examination of the cervical lymph node biopsy showed at Histologic sections. (a) effacement of normal architecture by a proliferation of lymphocytes with coarse chromatin with multiple areas of pallor consistent in proliferation centers (PC) exceeding ×20 field that become confluent in areas at low power (a; H&E ×20); (b)-(c) The histological sections at high power (H&E, ×40) show proliferation centers with increasing number of mitosis (red arrows) and of large cells including prolymphocytes and paraimmunoblasts (bleu arrows) among a dark background of abnormal small lymphocytes proliferation, at high power (H&E, ×40); (d) The Ki67 staining showed a high number of positive cells in the expanded centers exceeding 30% (H, ×40).

2.2. Case n°2

A 73-year-old female, with type 2 diabetes and atrial fibrillation, was diagnosed in May 2020 with stage B CLL. At diagnosis, the physical examination showed a patient with B symptoms, performance status at 2, and multiple cervical, axillary and inguinal lymph nodes. CBC showed white blood cell count 75,800/mm^3, 15% granulocytes, 85% lymphocytes, hemoglobin 12.5 g/dl and platelets 234,000/mm^3. She had high levels of lactate dehydrogenase at 573 UI/l ((reference range ≤270 U/L) and negative direct coombs test. The flow cytometry showed CD19+, CD5+, CD23+, low FMC7, low CD79b, low CD22, low CD20, CD43+, CD10− monoclonal B lymph proliferation with average expression of surface immunoglobulins type Kappa (Matutes score = 4). The research of the 17p deletion using FISH techniques was negative and the pursuit of TP53 mutation with PCR was not performed. Because of her heart failure, the patient received immunochemotherapy based on chloraminophen and Rituximab (Mabthera) without improvement of the tumor syndrome with progressive increase of the right axillary adenopathy measuring 6 cm of great axis. The biopsy of the right axillary lymph node revealed A-CLL. In fact, histologic funding showed an increase in confluent proliferation centers; the lymphoid proliferation was composed of small to medium sized lymphoid cells and larger immunoblastic-like cells, with enlarged nuclei. The cells were positive for CD20, CD23 and CD5, negative for cyclin D1 and with the Ki 67 index increased at the level of the proliferation centers, exceeding 40% (**Figure 2**).

Due to the unavailability of ibritunib treatment, the patient received 6 courses of R-COP (Rituximab, Endoxan, Oncovin and Prednisone) chemotherapy regimen and she died of tumor progression.

3. Discussion

A-CLL is a rare entity; it represents less than 1% of all reported cases of CLL. However, it is most likely an under diagnosed entity due to its rarity and the non standardized practice of lymph node biopsy in CLL. Moreover, the diagnosis of accelerated CLL is challenging because of the overlapping clinical features between A-CLL and RT [6]. Adequate diagnosis in patients with A-CLL is important for the management and the treatment choice.

The histological exam of the lymph node in CLL shows an infiltration of small monomorphic B cells. Proliferation centers can be absent or small with a low mitotic activity, containing prolymphocytes and para-immunoblasts and the proliferation index Ki67 in CLL is low (<40%). The cells express commonly CD5, CD23, FMC7 and sometimes they can express other B cells markers like CD20, CD19, and CD79a (score of the matutes) [7].

RT is characterized by a diffuse proliferation of large cells paraimmublasts mimicking centroblasts and more rarely immunoblasts, the expression of Ki 67 is more diffuse and is not limited to the proliferation centers [6] [8]. The CD23 expression was lower in RT compared to A-CLL [8] [9].

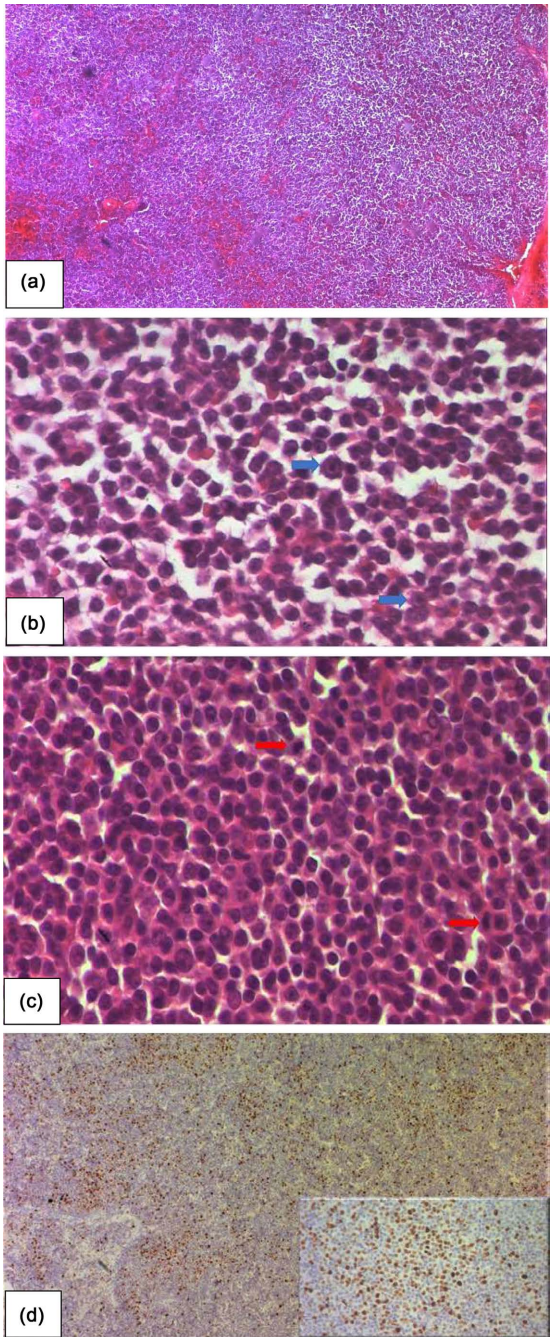

Figure 2. Right axillary lymph node biopsy showed the lymph nodes involved by Accelerated chronic lymphocytic leukemia. (a) The histological section at low power (H&E, ×20) showed effaced nodal architecture by a diffuse atypical lymphoid population of small to intermediate-sized cells with expanded proliferation centers that became confluent in areas; (b) On higher-power examination (H&E, ×40), increased paraimmunoblasts (bleu arrows) and prolymphocytes were observed within expanded Proliferated centers; however, there are no sheets of large cells to indicate histologic transformation to diffuse large B cell lymphoma; (c) Mitoses (red arrows), when present, are generally found associated with proliferation centers (H&E, ×40); (d) The Ki67 proliferation index was approximately 5% - 10% in the areas of smaller lymphocytes, with increased proliferation index of approximately 40% in the expanded proliferation centers (Ki67 (×10 (a), ×40 (b)).

A-CLL was defined as an intermediate subtype as it has features of both typical CLL and RT with a monotonous proliferation of small lymphocytes. In a study conducted by Gine and al. [5], the histological criteria of A-CLL were defined. The diagnosis of A-CLL requires the presence of at least one of three morphologic features which are the increase in proliferation centers' size (PCs) (wider than a 20× microscopic field), a high proliferation index (Ki67 > 40% per PCs) and an elevated mitotic activity (more than 2.4 mitotic figures in a PCs). Results from immunohistochemical staining revealed a stronger expression of CD23, CD20, IRF/MUM1, and CD71 in the PCs of both typical and A-CLL [10].

Clinical features were comparable in both CLL and A-CLL including performance status, the presence of B symptoms, clinical stage or bulky disease. While RT had more B symptoms, a poorer performance status and more extranodal sites involvement compared to CLL and A-CLL [5]. Our two patients had B symptoms and bulky disease. On the other hand, the biological results showed some differences; A-CLL was associated with more elevated LDH serum levels ($p = 0.01$), more elevated Beta-2 micro globulin and higher ZAP-70 levels expression in flow cytometry ($p = 0.014$) than CLL but comparable to RT [5]. The immunoglobulin heavy chain (IGVH) mutational status study, showed a non-mutated status in 100% of cases. Fluorescence in situ hybridization (FISH) revealed no difference in distribution of unfavorable cytogenetic abnormalities between the 3 groups (typical CLL, A-CLL and RT) [5]. Although, other reports showed that A-CLL was more probable to carry 17p and 11q deletions, TP53 mutation and complex karyotype, suggesting the poor prognosis of this entity [10] [11]. Furthermore, no specific radiographic findings have been shown to be specific for A-CLL. In fact, the positron emission tomography/computed tomography (PET/CT) is not specific because in both RT and A-CLL, the adenopathies are avid to fluorodeoxyglucose (18FDG) [12].

According to Gine and al study, A-CLL showed a poor prognosis (with a median survival after biopsy of 34 months) compared with CLL (the median survival after biopsy of 76 months) with a statistical significant difference ($p = 0.008$) while the difference between the prognosis of A-CLL and RT (with a median survival after biopsy of 4.3 months) was not significant ($p = 0.07$) [5]. This is particularly important, highlighting the different prognosis between these three entities and how the prognosis of A-CLL is intermediate between CLL and RT. Besides, the poor prognosis of this entity was suggested by a predominance of poor prognostic markers including an increasing number of p53-positive cases in A-CLL compared to standard CLL [5] [13] [14].

Given its poor prognosis, as showed in our two cases, the question is whether or not patients with A-CLL should receive immediate intensive treatment. To this date, no prospective study has been led to define the best treatment for A-CLL. In the study of Gine and al [5], the presence of extensive or highly active PCs had no influence on the treatment decision and therefore the treatment of patients with A-CLL varied over time. In the same report, patients received dif-

ferent types of treatment, 52% of patients received chemotherapy containing doxorubicin, 30% of patients received purine analogues, as a single agent or in combination and 73% of cases with RT were treated with doxorubicin regimens. As a result, resistance to doxorubicin was found in 29% of CLL, 50% of A-CLL and 33% of RT. In this study there was no comparison between the different chemotherapy regimens in the treatment of A-CLL [5].

As mentioned, the presence of deletion 17p has a poor prognosis and is known to be resistant to chemoimmunotherapy particularly regimens including purine analogs like FCR (Fludarabine-Cyclophosphamide-Rituximab) since the p53 is the mediator for the cytotoxicity of purine analogs. Data from a randomized German study showed that only 5% of patients having CLL with 17p deletion achieved complete remission after receiving FCR regimen [15]. Since A-CLL is more probable to carry 17p deletion, it is therefore refractory to conventional chemoimmunotherapy.

Bruton's tyrosine kinase inhibitors, like ibrutinib, have shown remarkable responses in relapsed/refractory CLL including those with an unfavorable cytogenetic profile. It improved survival rate comparing to chemoimmunotherapy. A study, focusing on the long term efficiency and safety of ibritunib in CLL, showed that after a follow up of 5 years the overall response rate was 89% and the complete response rate increased for both relapsed/refractory CLL and untreated CLL by 10% and 29% respectively [16]. The progression-free survival (PFS) rate was 9% in untreated CLL and 10% in relapsed/refractory CLL. Ibrutinib also improved the median PFS in patients with poor prognosis notably those with deletion 17p, deletion 11q and unmutated IGHV [16]. The role of ibrutinib in treating RT is still controversial, mainly because it provides short term efficacy. In some clinical trials, patients with RT were treated with ibrutinib. A complete response was achieved in 50% of cases and the median survival was short [17] [18] [19]. In a report of two cases, ibrutinib was used as a single agent treatment for A-CLL and managed to obtain a partial response for both patients [6].

Based on the lack of prospective studies, the best treatment for A-CLL is yet to be defined. The shorter survival of A-CLL when compared to typical CLL suggests the need of a more aggressive treatment. The question that stills remains to be answered is whether or not high-risk A-CLL patients should receive intensification with stem cells transplant. Finally, randomized studies are needed to explore the most effective treatment of this rare entity.

4. Conclusion

There are few reports on A-CLL as an intermediate phase between CLL and RT. Available data insists on the role of lymph node biopsy when a clinical transformation is suspected or in case of a refractory or relapsed disease. A-CLL should not be under diagnosed any longer given the easy clinical and histological features while adapted treatment still needs to be improved by conducting prospective studies for ideal management and outcome in A-CLL. It should be suspected

when the patient presents a fast enlargement of lymph nodes with either a relapse or a drug-resistant disease, as was reported in both of our patients.

Ethical Approval

This study was approved to be in accordance with standards for good scientific practice by the Committee for Research Ethics at Farhat Hached University Hospital, Tunisia (Ref: CER: 29-2023).

Conflicts of Interest

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

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