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CD2+ hairy cell leukemia

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Introduction

Hairy cell leukemia (HCL) is an uncommon mature B-cell neoplasm, accounting for only 2% of all lymphoid leukemias [1]. In recent years, clinical and immunophenotypic subtypes of HCL have been described, such as hairy cell leukemia variant (HCL-v) [1] and hairy cell leukemia Japanese variant (HCL-jv) [2, 3]. In the next (5^{th}) edition of the World Health Organization Classification of Hematolymphoid Tumors, the term 'splenic B-cell lymphoma/leukemia with prominent nucleoli' will probably replace the term 'hairy cell leukemia variant' [4].

Here, we present the case of a patient with an abnormal expression of the T-lineage antigen CD2 in HCL cells. To the best of our knowledge, fewer than 10 cases of CD2+ HCL have been described worldwide [5–7].

Case description

A 43-year-old man was referred to our laboratory for bone marrow aspiration and immunophenotyping for leucopenia and thrombocytopenia detected in a complete blood count (CBC), as part of routine medical exams. He had no lymphadenopathy, hepatomegaly, or splenomegaly. Hematological parameters were: hemoglobin (Hb) — 15.0 g/dL; hematocrit (Ht) — 43.1%; white blood cells (WBC) — 2.09×10^9/L (neutrophils — 47.6%, monocytes — 1.4%, lymphocytes — 47.8%, basophils — 0.5%, eosinophils — 2.7%); platelets (PLT) — 90×10^9/L. The blood smear revealed the presence of 3% small to medium-sized lymphoid cells characterized by a nucleus with moderately condensed chromatin without nucleoli, and slightly basophilic cytoplasm devoid of granules and exhibiting thin and elongated hairy projections. Erythrocyte sedimentation rate (ESR) — 3 mm and lactate dehydrogenase (LDH) — 179 U/L (normal range).

A bone marrow aspirate was performed. There were no technical difficulties in the procedure. The bone marrow smear showed the presence of 7% of atypical lymphoid cells characterized by a nucleus with homogeneous chromatin and a pale-blue cytoplasm exhibiting thin and elongated hairy projections, a finding similar to that seen in the blood film. A bone marrow trephine biopsy was not performed. The reason, however, why the trephine biopsy was not performed is not available to us.

The presence of two distinct subtypes of B-lymphoid cells (CD19+) was revealed by flow cytometry analysis of the bone marrow (Figure 1A). The 'green population' ($CD19^{moderate}$, gate 'L') — characterized by SSC^{dim}, CD2–, $CD20^{dim}$, CD22+, CD23+, CD103–, CD200–, and polyclonal kappa+ and lambda+ (Figure 1) — had the phenotype of normal B-lymphocytes. On the other hand, the 'red population' ($CD19^{bright}$, gate 'K') — characterized by SSC^{bright}, CD20+, CD22+, CD23–, CD103+, CD200+, and kappa+ light-chain restriction (Figure 1) — and, moreover, CD10–, $CD11c^{bright}$, CD25+, $CD45^{bright}$, CD79b–, CD123+, and FMC7+ (data not shown) had the typical phenotype of hairy cell leukemia.

Interestingly, the HCL cells exhibited positivity for the antigen CD2 (clone: RPA-2.10) (Figure 1B, C), though the cells did not express other T- and natural killer (NK)-lineage markers (CD3–, CD4–, CD5–, CD7–, CD8–, CD16–, CD56–) (data not shown). The HCL population was practically all positive for CD2, with few HCL cells ('red events') in quadrants 1 and 3 (CD2 negative cells) of the dot-plot 'B' (Figure 1).

Based on clinical and laboratory data, a diagnosis of HCL with atypical expression of CD2 antigen was made. The patient was submitted to monotherapy with chimeric anti-human CD20 antibody (rituximab) 375 mg/m^2 intravenously for three months. After completion of the treatment, a CBC evidenced improvement in leucocyte and PLT counts:

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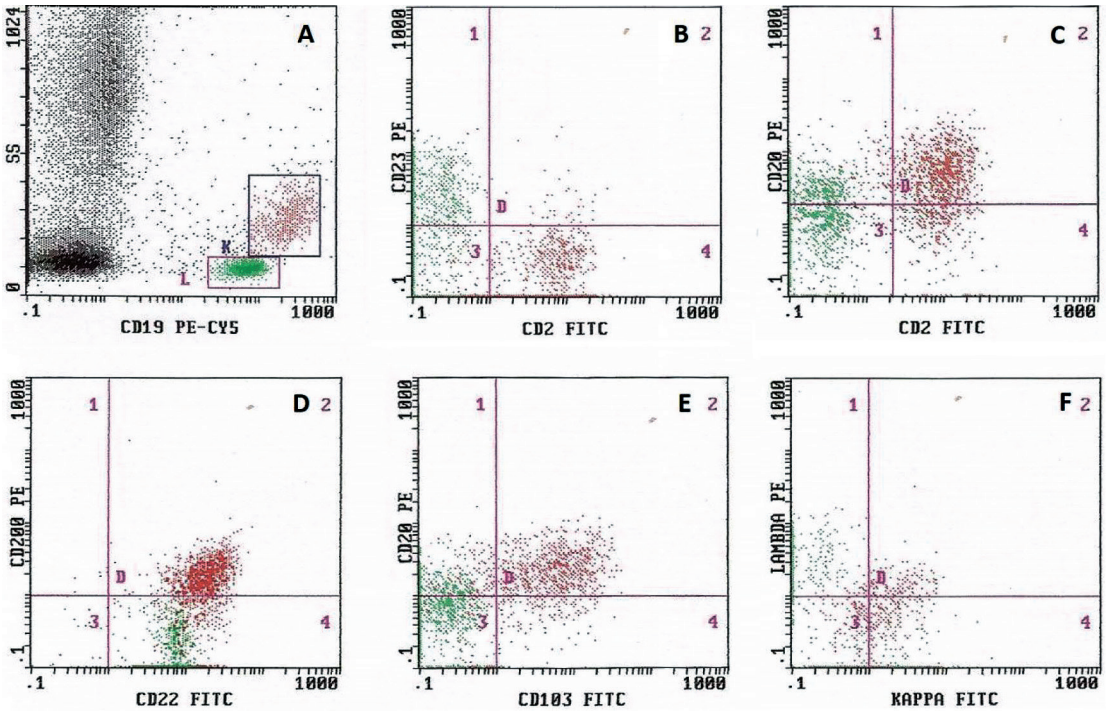

Figure 1. Flow cytometry findings of patient's bone marrow: **A.** The physical parameter (SCC) and CD19 expression show the presence of two distinct populations of B-lymphoid cells (red: HCL cells; green: normal B-lymphocytes); **B, C.** CD2 positivity on HCL cells; **D, E.** HCL cells show positivity for CD20, CD22, CD103, and CD200; **F.** Kappa light-chain restriction of HCL cells

Hb — 15.0 g/dL; Ht — 43.2%; WBC — 4.2 × 10^9/L (neutrophils — 69%, monocytes — 4.3%, lymphocytes — 25.1%, basophils — 0.5%, eosinophils — 1.1%); PLT — 130 × 10^9/L. No atypical lymphoid cells were found on blood smear.

The patient was therefore referred for bone marrow aspiration and minimal residual disease (MDR) evaluation by flow cytometry. The bone marrow aspirate showed 0.3% of atypical lymphoid cells, morphologically similar to those found in the diagnosis. MDR analysis revealed the presence of CD2 once again (0.34% of CD2+ HCL cells in the bone marrow) (data not shown). This data rules out any possibility of eventual technical errors in the identification of CD2 at diagnosis and seems to indicate that the antigen is useful for the detection of minimal residual disease.

Discussion

Preliminary data has shown that the expression of CD2 in HCL could be as high as 25% [6]. However, this was certainly an overestimate of the actual percentage because that data came from a report of only three CD2+ HCL cases out of 12 classical HCL [6]. More recently, Shao et al. [7] studied 169 HCL patients and found only three cases (2%) of CD2+ HCL.

Therefore, given that HCL is a rare disease, accounting for only 2% of lymphoid leukemias, CD2+ HCL is an extremely rare clinical condition, accounting for approximately 0.04% of all lymphoid leukemias. CD2 is also variably expressed in other mature B-cell neoplasms, such as chronic lymphocytic leukemia (16%), large B-cell lymphomas (29%), and follicular lymphoma (55%) [6].

An unusual clinical aspect of this case was the absence of splenomegaly. Kurosawa et al. [5] reported a single CD2+ HCL patient exhibiting only discrete splenomegaly (3 cm below left costal margin). Unfortunately, Kingma et al. [6] and Shao et al. [7] did not report data concerning the presence or absence of splenomegaly in their series.

Another curious feature is that, if it could be shown that the abnormal cells exhibited monoclonality for the T-cell receptor (*TCR*), it could be determined that the leukemic cells belonged to a dual lineage (B and T: 'bilineage' HCL), which cannot be presumed with the isolated presence of the CD2 antigen. However, unfortunately the patient was not submitted to *TCR* rearrangement studies. Kingma et al. [6] employed polymerase chain reaction (PCR) analysis for the determination of *TCR* gamma gene rearrangements in 2/3 CD2+ HCL patients. In both cases, the *TCR* was germ line.

The prognostic significance of CD2 in mature B-cell neoplasms remains to be elucidated. Inaba et al. [9] studied three patients with CD2+ B-cell non-Hodgkin's lymphoma, and showed extranodal involvement at diagnosis in all the cases. Suzuki et al. [10] showed the expression of CD2 in 2.7% of patients with the diagnosis of diffuse large B-cell lymphoma. The expression of CD2 did not appear

to be related to any clinicopathological features or survival [10]. Given the rarity of CD2 expression in HCL, no data exists on the clinical significance of CD2 positivity in this disease.

Significantly, at the present time it also remains unknown whether the abnormal expression of CD2 simply represents a variant phenotype of HCL or, alternatively, whether these cases are truly distinct clinical entities, like the HCL variant that, while resembling classic HCL, exhibits different cytological and immunophenotypic features, as well as diverse sensitivity to therapeutic agents effective in HCL. Following this train of thought, given that previous data showed that CD2+ B-lymphocytes represent a normal cellular population within the peripheral blood (approx. 3.6% of B-cells), it is not far-fetched to speculate that this small population of CD2+ B-lymphocytes could be the benign counterparts of some subtypes of CD2+ mature B-cell leukemias/lymphomas [6, 8].

The identification of more HCL patients with abnormal expression of CD2 — and, hence, the availability of a greater amount of clinical, immunophenotypic, cytogenetic, and histological data — is necessary to address these issues. It seems that the use of an extensive flow cytometry panel, including T- and NK-lineage markers, is appropriate for the immunophenotyping of HCL.

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Author's contributions

DMM — sole author.

Conflict of interest

The author declares no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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