

Acute Lymphoblastic Leukemia cured without treatment – is that so?

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Abstract: Spontaneous remission of acute lymphoblastic leukemia is an extremely rare phenomenon. It usually occurs in an aleukemic prodromic setting associated with cytopenias and fever. Nonetheless, this remission status, as far as we know, is always transient, the longest one described lasting one year. In this case report, we present a 25-months year-old boy with de novo bruises. His complete blood count displayed thrombocytopenia and leukopenia, and biochemistry analysis an increased lactate dehydrogenase. Although bone marrow aspirate was unremarkable, trephine biopsy was suggestive of B-cell acute lymphoblastic leukemia. Within three months, however, he showed a spontaneous clinical and analytical recovery. A repeated biopsy performed two years after was also completely normal. At the time of the writing of this paper, seven years later, the child remains free of progression. It might be the longest spontaneous remission ever described. Oppositely, some histology reports added a differential diagnosis - that the 24.49% immature B-cell infiltrate could, as well, resemble B-hematogones. Hence, we herein try to unveil the mechanism under this phenomenon. More efforts should be directed towards research about pre-acute lymphoblastic leukemia and spontaneous remission, so that pediatricians and pathologists can be more comfortable with these rare, but very challenging, situations.

Keywords: B-cell acute lymphoblastic leukemia; Pre-acute lymphoblastic leukemia; Spontaneous remission; Hematogones.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, accounting for approximately 25% of all cancers in children up to 15 years old. When left untreated, its natural history is that of uncontrolled proliferation of neoplastic lymphoblasts, resulting in decreased production of normal functional hematopoietic cells, ultimately leading to progressively worsening anemia, bleeding, infection, and fatal organ failure [1].

Spontaneous remission (SR) is defined by a partial or complete disappearance of a malignant disease, either without initiating any specific treatment or under therapy which is not, however, considered efficient enough to exert a significant influence on the disease course [2]. It is an extremely rare phenomenon, usually occurring in a rapid but always

transient manner. The mechanisms by which SR occurs are not fully understood, although patients usually present with fever or sepsis concomitantly. In fact, SR has already been documented in several types of cancer, most frequently in melanoma, neuroblastoma, nephroblastoma and lymphoma. [3] Transient SR of acute lymphoid and myeloid leukemia has also been reported, but all cases described in the literature are, indeed, inevitably followed by relapse [4]. In ALL, the prevalence of SR may be as high as 4%. Nevertheless, one should keep in mind that the overall incidence of ALL is low (despite being the most frequent pediatric cancer) and such cases are even less commonly observed with the advent of highly effective therapies [5].

However, SR usually occur in an aleukemic prodrome setting (pre-ALL). This condition is mostly described in childhood ALL-B (in about 2% of cases), especially of the common immunophenotype. Most patients are female, and present with fever, fatigue and a hypoplastic bone marrow or cytopenias, usually in association with an infectious status (like patients with SR). Then, it either spontaneously resolves or is very responsive to corticosteroids, although, once again, this latency only lasts up to one year according to the literature [6, 7, 8, 9]. Indeed, pre-ALL not only closely resembles SR, but both conditions might even represent a single disease entity [10].

Herein, we report a case of ALL followed by a spontaneous and lasting remission, without any treatment, currently for more than seven years.

2. Case Report

A previously healthy 25-months year-old boy was transferred to Pediatric Oncology Service of Portuguese Oncology Institute of Porto (IPO Porto) in July 2015, presenting with one month and a half lasting bruises scattered throughout all his body, even in areas non-susceptible to trauma, and progressively worsening in number and dimension. No other symptoms were associated, namely weakness, fatigue, recurrent infections, or other bleeding signs. There was no previous exposure to drugs or toxins, neither recent foreign travel. Family history was unremarkable, as well. Physical examination revealed mild pallor, petechiae, and infra-centimetric cervical and inguinal lymph nodes. There was no hepatosplenomegaly nor dysmorphic features.

Laboratory results showed bicytopenia (thrombocytopenia below 10.000/uL plus leukopenia, with both lymphopenia and neutropenia, the later persistently below 1.000/uL). Blood biochemical analysis was unremarkable, apart from lactate dehydrogenase (LDH) of 519 IU/L (reference value: 105-333 IU/L), increased IgG and, opposingly, mild IgM deficiency. Uric acid, vitamin B12 and folate were normal; coagulation tests and viral serologies (Human Immunodeficiency Virus, Hepatitis C and B Virus, Cytomegalovirus, Epstein-Barr Virus and B19 Parvovirus) were unremarkable. Peripheral blood flow cytometry only identified decreased number of CD4+ cells. To search for the presence of organomegalies, cervical and abdominal ultrasound were performed, and neither hepatosplenomegaly nor lymph nodes fulfilling the criteria for pathological adenomegalies were disclosed.

As part of the diagnostic workup in a patient presenting with unexplained cytopenias, serial myelograms were performed. The first showed a relative increase in monocytic lineage with some immaturity. Immunophenotyping identified an increased monoclonal population of $\gamma\delta$ T cells, but no signs of malignancy. Cytogenetics and molecular genetics were also negative for common chromosomal translocations, such as BCR-ABL1, ETV6-RUNX1, KMT2A-AFF1 and TCF3-PBX, as well as other translocations involving KMT2A gene, numerical abnormalities of chromosome 21 and RUNX1 gene amplification. Finally, bone trephine biopsy assessment disclosed normocellular hematopoietic bone marrow with an increased reticulin fiber meshwork (MF-2) and decreased maturation of myeloid lineage, although with no dysplastic features. There was, however, a lymphoid interstitial infiltrate, composed of small to intermediate size cells, with scant to moderate cytoplasm

and immature, granular chromatin, immunophenotypically resembling immature B cells (Tdt +, focally CD34+, CD20+, CD3-, MPO-, CD68-) (Figure 1). Thus, a diagnosis of precursor B-cell ALL was suggested.

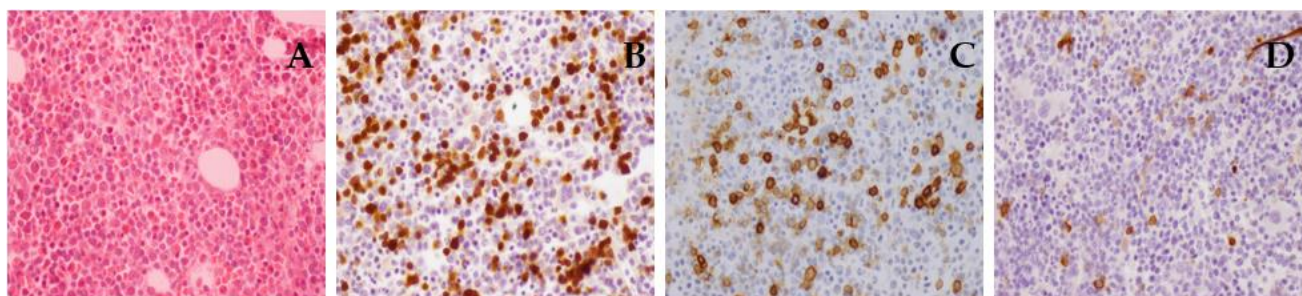


Figure 1: Bone marrow trephine biopsy at diagnosis (July 2015). Hematoxylin-eosin (HE) staining displaying an interstitial-pattern lymphoid infiltrate, constituted by small to intermediate cells, with scant cytoplasm, loose and finely granular chromatin (A). Immunohistochemistry staining showing the distribution of TdT (B), CD20 (C) and CD34 (D).

A second bone marrow aspirate was then obtained two weeks later. In this sample, immunophenotyping identified a population of 24.49% B cell precursors, in all maturation stages, suggestive of hematogones (HG). It was repeated, again, one month later, and although the aspirate, this time, had not shown any signs of disease, histology report was, on the other hand, like the previous one, with the addendum that those immature B cells could also be either blasts or HG (Figure 2).

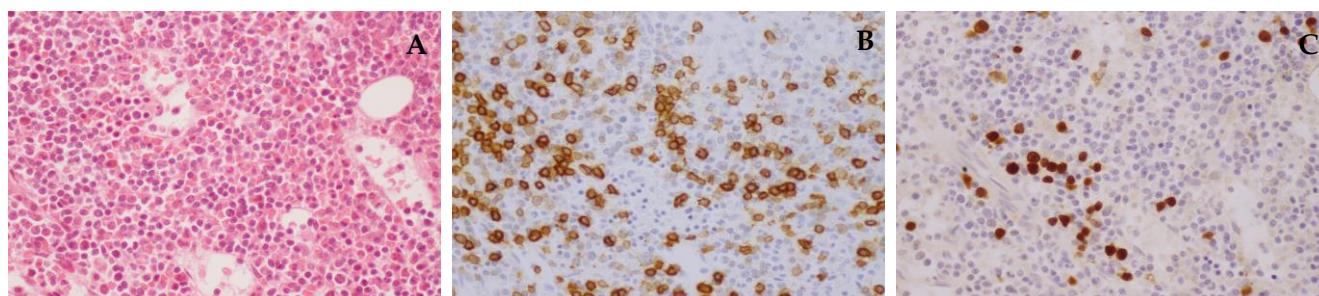


Figure 2: Second bone marrow trephine biopsy (August 2015). HE staining displays also a lymphoid infiltrate resembling the one from previous biopsy (A); however, this time, histological report added the possibility that those cells could be B hematogones instead of lymphoblasts. Immunohistochemistry staining showing the distribution of CD20 (B) and TdT (C).

Interestingly, from July to October 2015, there was a significant, and spontaneous, clinical and analytical improvement. Petechiae and bruises disappeared, with no other signs of bleeding, and there was no record of infection. Leukocytes and neutrophils values normalized, followed by platelets (absolute neutrophil count of 5590/uL and platelets of 191.000/uL). Other two bone marrow samples were obtained after approximately 6 and 12 months, and they kept showing involvement by the same ambiguous cell population. Finally, two years later, another sample obtained for follow-up purposes was reported as having no atypical lymphoid infiltrate.

The child kept an assiduous follow-up at IPO Porto for more than seven years now, completely free of progression.

3. Discussion

Although this child had a clinical presentation and bone marrow suggestive of ALL, there was not a clear population of more than 20% of lymphoblasts in the bone marrow, required to establish this diagnosis. Taking this into account, it is likely that the patient presented, instead, a pre-ALL. And this case is of particular interest due to its very long-lasting remission status. It might even be the first clinical report of a non-relapsing pre-ALL, as after searching in Pubmed titles and abstracts with the keywords “pre-ALL”, “ALL prodrome” and “ALL spontaneous remission”, the maximum length of remission was one year.

Although extremely rare, SR/pre-ALL cases have, indeed, been reported, both in pediatric and adult patients. Sohn et al. reported two cases of adult ALL presenting with a pre-leukemic prodrome characterised by pancytopenia and a few abnormal lymphoid cells in bone marrow aspirate, thus suggesting the diagnosis of aplastic/hypoplastic anemia. However, both cases ended up progressing to overt ALL within 1 year [3]. Similarly, Vergara-Lluri et al. described six adult males presenting with a probable pre-ALL which also eventually progressed, with a very short median of time-to-progression of 2.5 months [12].

Regarding pediatric population, Hassle et al. identified eight children (2% of all cases of childhood ALL) with pre-ALL, whose bone marrow biopsies showed increased reticulin fibrosis and no cytogenetic abnormalities, such as the case herein described. However, again, eventually all of them progressed and, at the time of progression, in four of the six examined children, cytogenetic abnormalities were found [13]. According to Ford and colleagues, despite SR, the existence of pre-leukemic stem cells might constitute a persistent endeavored reservoir for relapse [14].

Although no genetic abnormality was found in our case, Zimmermannova et al., in turn, were able to identify one pre-ALL patient with the ETV6-RUNX1 translocation, probably an early genetic event. Moreover, ninety-two days before diagnosis, all analysed cells had deletion of non-translocated ETV6 and 14q24 alleles (167/167 and 5/5 cells, respectively). Other additional genetic aberrations were then identified at the time of diagnosis [15].

Favoring this prodrome-SR-relapse course, measurable minimal residual disease (MRD) in pre-ALL patients, determined by polymerase chain reaction analysis of immunoglobulin/T-cell receptor gene rearrangements, followed an “M-pattern” instead of a linear progression (initial high levels, followed by a significant decrease and, again, another rise at the time of the diagnosis) [16]. However, it can be difficult to establish the diagnosis of pre-ALL, as it very much resembles aplastic anemia. Nonetheless, bone marrows of patients with pre-ALL or SR usually show some differentiating features such as fibrosis and lymphocytic infiltrates, especially of T cells, which is in accordance with the case herein presented [16, 17].

Curiously, bone marrow immunophenotyping and molecular biology analysis showed an increased population of $\gamma\delta$ T cells. In fact, the V γ 9V δ 2 cells (the most abundant subset of circulating $\gamma\delta$ T cells) may exert an immunosurveillance role in pre-ALL by recruiting other much more cytotoxic cells, especially natural killer cells [18]. This cytotoxic reaction involving $\gamma\delta$ T cells, which may cause a reduction of leukemic clones and, consequently, eradicate MRD and prevent future relapse, can be triggered by acute infection. This, in turn, might explain why these temporary SR were described in patients presenting with fever [19, 20]. Although this patient had two isolated febrile peaks, they were self-limited and associated with IgEV and platelets pool infusions.

Nevertheless, histopathology ended up suggesting an alternative hypothesis - that the immature cells detected both in flow cytometry and histology were B-HG instead of lymphoblasts (LB). HG is the term used to describe normal precursor lymphoid cells found in the bone marrow of normal people, especially infants and young children, as

their number declines with age. Morphologically and immunophenotypically, they may be very similar to LB, with the following immunophenotype - CD10+, CD19+, weak CD45+, sIg-, CD20- and CD123-. More recently, a group of investigators tried to find a multiparameter flow cytometry tool which might help to differentiate between them. They were able to demonstrate that a mean fluorescence intensity ratio of CD81/CD58 could address this problem (with an area under the curve of 0.995), as LB overexpress CD58 in detriment of CD81, in comparison with HG [21].

Usually, HG are found in a relative percentage inferior to 1%. However, their number can surpass 5% in some pathological conditions such as lymphoproliferative diseases, viral infections, post-chemotherapy, or post-hematopoietic stem cell transplantation or as a reactive phenomenon secondary to cytopenias of other causes (congenital, autoimmune) [22,23]. In this child, the only other possible cause for this hyperproliferation would be a transient viral aplastic anemia. However, they usually self-resolve within one or two weeks (not in 3 months as occurred in this case) and as previously explained, bone marrow histology would not preferentially show increased reticulin deposit [23]. A possible explanation is that LB and HG might co-exist, with the later appearing because of the lymphoproliferative disease.

A limitation of the study is the absence of a more complete genetic examination. In a future perspective, adding exome analysis might highlight additional or new findings about this rare condition, especially in cases without cytogenetic alterations.

4. Conclusion

This case report describes a patient who is likely experiencing a distinctive form of pre-ALL and has remained in spontaneous remission for over seven years. Pediatricians need to be aware of this phenomenon, as there is a high probability that it will eventually progress to ALL. Further efforts should be directed toward investigating the genetic profiles of these entities, which likely constitute the same disease continuum, contributing, in turn, to the ongoing research into the intricate interactions among the immune system, hematopoiesis, and the development of leukemia.

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