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Case Report

Relapsed/refractory pure red cell aplasia in chronic lymphocytic leukemia successfully treated with acalabrutinib: a case report and review of the literature

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Alberto Fresa, Idanna Innocenti, Annamaria Tomasso, Luca Stirparo, Antonio Mosca, Francesco Iadevaia, Francesco Autore and Luca Laurenti

***Abstract*:** The incidence of pure red cell aplasia (PRCA) in chronic lymphocytic leukemia (CLL) is <1% and treatments include the use of steroids and therapeutic strategies including immunosuppressive therapies. Here we present a case of a CLL-associated PRCA successfully treated with acalabrutinib, a treatment never described before for this specific condition, obtaining a rapid response after failing two lines of therapy. Exploring the treatment rationale, both the immune modulation and the continuous control of the disease, could have played a role in the treatment efficacy. Covalent BTK inhibitors are an effective treatment option for autoimmune complications of CLL, including CLL-associated PRCA.

Keywords: acalabrutinib, case report, chronic lymphocytic leukemia, pure red cell aplasia

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Correspondence to:
Luca Laurenti
Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy

Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli 8, 00168, Rome, Italy
luca.laurenti@unicatt.it

Alberto Fresa
Annamaria Tomasso
Luca Stirparo
Antonio Mosca
Francesco Iadevaia
Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy

Idanna Innocenti
Francesco Autore
Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Alberto Fresa is also affiliated to Hematology-Oncology and Stem-Cell Transplantation Unit, Department of Onco-Hematology and Innovative Diagnostics, Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale, Napoli, Italy

Introduction

Pure red cell aplasia (PRCA) is a bone marrow (BM) disorder characterized by normocytic anemia and reticulocytopenia caused by the destruction of erythroid precursors. The incidence of PRCA in patients with chronic lymphocytic leukemia (CLL) is <1% and can present with or without concomitant autoimmune hemolytic anemia (AIHA).[1] Treatments for PRCA in CLL include first the use of steroids, intravenous immunoglobulins (IVIG) in case of hypogammaglobulinemia, and then therapeutic strategies including immunosuppressive therapies (e.g., rituximab, cyclophosphamide, methotrexate).[2]

Here we present a case of a CLL-associated PRCA successfully treated with acalabrutinib after failing two lines of therapy. The reporting of this study conforms to the CARE statement (Supplemental Material).[3]

Case presentation

A 54-year-old man found normocytic anemia and lymphocytosis on examinations due to dyspnea for moderate exertion. The complete blood count at diagnosis was hemoglobin (Hb) 8.5 g/dl, mean corpuscular volume (MCV) 105.2 fl, hematocrit (Hct) 25.6%, platelet count (Plts) 337,000/μl, white blood cells (WBC) 16,300/μl, neutrophils (ANC) 2730/μl, lymphocytes (ALC) 9900/μl, mature lymphocyte elements and Gumprecht shadows, and reticulocytes 1.0%. He presented with normal levels of lactate dehydrogenase, bilirubin, serum iron levels, ferritin, transferrin, folate, vitamin B12, and thyroid function. Assessments for hemolysis revealed negative direct and indirect Coombs test, cold agglutinins, and irregular antibodies; haptoglobin levels were slightly reduced (80 mg/dl, normal value >100 mg/dl). Immunoglobulin (Ig) levels were normal: IgG 760 mg/dl, IgA 90 mg/dl, IgM 43 mg/dl. Hepatitis B virus (HBV), hepatitis C virus (HCV),

Parvovirus B19 serologies, and viremias were negative for previous or current infection. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) serologies and viremias were positive for previous infection and negative for current infection.

CLL was diagnosed with 8-color flow cytometry which revealed a 71% B-cell population that was CD5/CD19/CD200/CD23/CD43 positive, CD20 dim, and CD10/CD79b negative.

On physical examination, he presented with a normal performance status, but reduced tolerance to mild-to-moderate exertion, palpable splenomegaly (3 cm from arch), and lymph nodes (maximum 2 cm in left axillary cord).

Therefore, he performed a BM examination which confirmed the diagnosis of PRCA (erythroid series 1%, lymphocytes 79.5%, granulocytic series 19%, and monocytic series 0.5%) and a total body computed tomography (CT) scan which confirmed splenomegaly (transversal diameter 14 cm) and enlarged lymph nodes (maximum 4.7 cm interportocaval) and excluded the presence of other pathological conditions related to PRCA (i.e., thymoma).

Biological analysis on peripheral blood revealed the following: unmutated immunoglobulin heavy chain (IGHV) gene; absence of del17p, del11q, del13q, and tris12 at Fluorescence In Situ Hybridization (FISH) analysis; at next-generation sequencing analysis TP53 wild type, NOTCH1 mutated (three mutations), BIRC3 mutated (two mutations), and SF3B1 wild type.

Immediately after performing a BM examination and CT scan, the patient started first-line treatment with prednisone 1 mg/kg; at that time, he was transfusion dependent, with a baseline transfusion burden of 1–2 red blood cells (RBCs) units per week.

No substantial improvement was observed after 2 weeks of steroid therapy, so the patient underwent second-line treatment with four weekly administrations of rituximab 375 mg/mq from July 11, 2023. The best response obtained was a partial response registered after the third rituximab administration (Hb 11.1 g/dl), but transfusion independence only lasted 3 weeks after the end of treatment.

After the failure of the second line of therapy, the patient started CLL-directed treatment with acalabrutinib 100 mg twice a day on September 14, 2023. After 2 weeks of treatment, the patient achieved transfusion independence, manifesting reticulocytosis (2- and 3-week reticulocyte counts were 306,000/μl and 175,000/μl, respectively) and progressive increment of Hb levels (2-, 3-, and 6-week Hb was 8.8, 10.8, and 12.5 g/dl, respectively). The trend of Hb levels and reticulocyte count according to treatments is shown in Figure 1. No adverse event is currently reported after 6 months of treatment, and the patient is still in response (complete blood counts in Table 1).

Discussion

This is the case of a patient with CLL-associated PRCA treated with acalabrutinib, a treatment that has never been described before for this specific condition. The diagnosis of PRCA can be difficult, and identifying the cause of PRCA can be even more challenging. Generally, it is a diagnosis of exclusion for AIHA, drug toxicity, or other immune disorders. In this specific case, the diagnosis was made through the combination of anemia, reticulocytopenia, and suppressed erythroid series at the BM examination, together with normal levels of iron and vitamins and the absence of hemolysis, thereby meeting the current recommendations for the diagnostic workup.

After a diagnosis of PRCA, other causes that may trigger PRCA must be excluded. These include Parvovirus B19 infection, hypogammaglobulinemia, T-cell large granular lymphocyte leukemia (LGL), thymoma, and good syndrome (i.e., hypogammaglobulinemia and thymoma). Understanding the pathogenesis of PRCA is critical for developing therapeutic strategies. Idiopathic PRCA is the most frequent form of acquired PRCA, probably due to the destruction of erythroid precursors mediated by cytotoxic T cells.[2] Causative antibodies should recognize antigens present only at the level of erythroid precursors and absent on erythrocytes. PRCA associated with hypogammaglobulinemia implies that antibody responses or T-cell receptor (TCR) recognition failure may lead to overexpressed cytotoxic T-lymphocyte responses with cross-reactivity against erythropoiesis.[2] Alternatively, deficient humoral responses due to hypogammaglobulinemia may result in viral persistence or inability to clear infectious agents with direct toxicity or

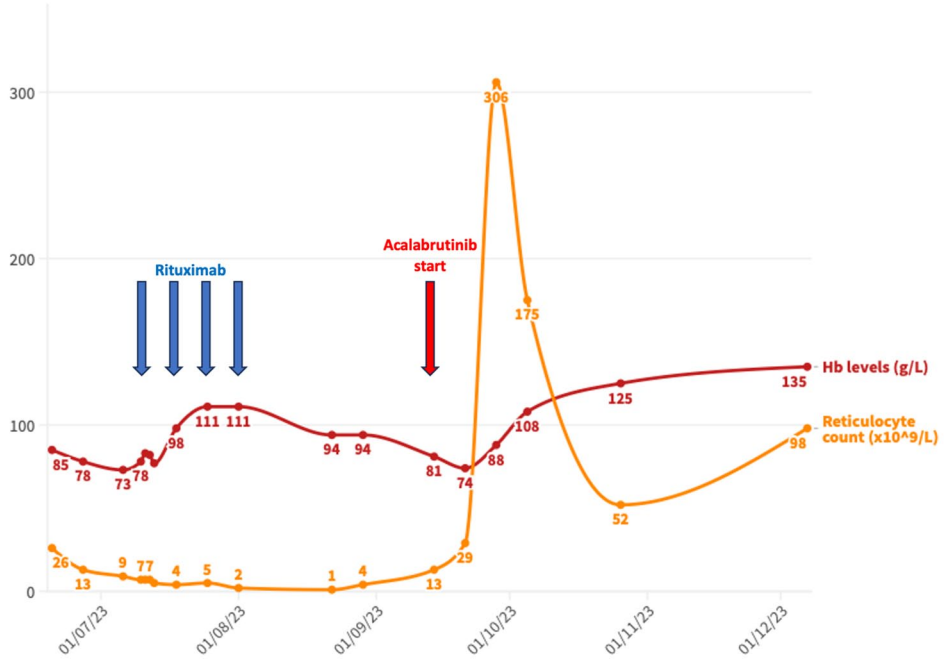

Figure 1. Trend of hemoglobin levels and reticulocyte count according to treatments.

induction of polyclonal T-cell cross-reactive responses. It is possible that cases of PRCA associated with B-cell lymphoproliferative disorders are due to disease-intrinsic or iatrogenic hypogammaglobulinemia. The occasional responsiveness to IVIG has not been fully elucidated and could involve the elimination of a cryptic viral trigger or masking of autoimmune epitopes, as with immune thrombocytopenic purpura. In our case, since hypogammaglobulinemia and viral infections were excluded at diagnosis and no other pathological conditions were detected on a CT scan, we hypothesized that the trigger of PRCA was immune-mediated. Once other causes are excluded, the main pathogenetic mechanism of PRCA in CLL is considered to be the suppression of erythropoiesis by T cells or NK cells.[2] However, although in idiopathic PRCA, T-lymphocytes are the main candidate effectors, this may not necessarily be true for all CLL-associated PRCA. In fact, humoral immunity might be involved in this context, as demonstrated by the presence of antibodies against RBC precursors in some PRCA patients. This hypothesis seems realistic, especially in the context of CLL-associated PRCA, in which alteration of B cells (belonging to the neoplasm or other clones) is intrinsic to the pathophysiology of the disease. This observation is supported by the common finding of additional autoimmune B-cell disorders in B-CLL patients.[2]

According to the current recommendations, frontline treatment should include immunosuppressive therapies.[2] Apart from steroids, most of the reported cases of PRCA in CLL were treated with four weekly administrations of rituximab, mostly with good results.[4] Other reports of lymphoproliferative diseases include cyclosporine, methotrexate, cyclophosphamide, and other immunosuppressive agents in T-LGL-associated PRCA; bortezomib in plasma cell dyscrasias; and alemtuzumab in CLL.[2] Growing evidence is emerging regarding the efficacy of covalent Bruton Tyrosine Kinase inhibitors (cBTKi) for the treatment of autoimmune complications of CLL, both as monotherapy and in combination with rituximab.[5,6] To the best of our knowledge, only five cases of PRCA have been reported in the literature treated with ibrutinib, and none of the patients were treated with acalabrutinib or zanubrutinib. In our case, the assumption was to treat the underlying condition, thus stopping the trigger of the PRCA, as for other autoimmune

Table 1. Trend of CBC values from diagnosis to the last follow-up.

Date	Hemoglobin (g/l)	MCV (fl)	Reticulocyte count ($\times 10^9$/l)	Platelet count ($\times 10^3$/μl)	WBC ($\times 10^3$/μl)	ANC ($\times 10^3$/μl)	ALC ($\times 10^3$/μl)
20/06/23	85	100.2	26	337	19.7	4.33	14.18
27/06/23	78	98.5	13	393	21.96	3.71	17.48
06/07/23	73	99.4	9	353	18.57	3.37	14.35
10/07/23	78	91.5	7	290	15.08		
11/07/23	83	92.3	7	272	15.36		
12/07/23	82	94.5	7	281	13.41		
13/07/23	77	94.6	5	226	10.3		
18/07/23	98	95.5	4	453	30.53	10.65	18.71
25/07/23	111	98.5	5	329	12.58	5.34	6.62
01/08/23	111	100.8	2	215	7.34	2.57	4.18
22/08/23	94	95.3	1	575	6.8	3.14	3.05
29/08/23	94	88.4	4	492	9.19	4.94	3.58
14/09/23	81	88.7	13	560	10.72	6.78	3.15
21/09/23	74	90.4	29	502	11.22	6.31	4.14
28/09/23	88	92.3	306	666	14.14	7.63	5.8
05/10/23	108	96.5	175	523	10.13	5.84	3.45
26/10/23	125	93.3	52	293	8.65	5.17	2.96
07/12/23	135	88.8	98	397	10.22	4.97	4.05
02/02/24	134	86.1	87	275	5.62	4.04	1.83

cytopenias, and in accordance with current guidelines.

Our choice to use acalabrutinib in such a young patient mostly relied on the low burden of adverse events registered with long-term continuative treatment compared with ibrutinib. A possible limitation of the use of acalabrutinib in this setting compared with other covalent BTK inhibitors is its more selective mechanism of action. In fact, ibrutinib and zanubrutinib on-target off-tumor mechanisms of action inhibit the Tec family of non-receptor tyrosine kinases (TFK), especially interleukin-2 inducible tyrosine kinase (ITK) expressed in T cells and NK cells. This inhibition leads to the inactivation of Th2-cells and the inhibition of antibody-dependent cellular cytotoxicity, making these two molecules active against both the humoral and cellular immune pathogenetic pathways of AIHA.[7] Nevertheless, in our case, the absence of concurrent AIHA and the initial partial response to rituximab guided our decision to prioritize the continuous control of the disease with the currently safe and effective covalent BTK inhibitor, instead of T-cell modulation.

Conclusion

Covalent BTK inhibitors are an effective treatment option for autoimmune complications of CLL, especially AIHA. CLL-associated PRCA,

a cinderella of autoimmunity, could follow the same indications of other CLL-associated AIHA, currently suggesting cBTK inhibitors as the best second-line treatment. Clinical trials evaluating frontline targeted therapy for CLL-associated autoimmune cytopenias are needed to better understand the best treatment choice for each clinical manifestation.

Declarations

Ethics approval and consent to participate

The study was conducted according to the Helsinki Declaration, Good Clinical Practice, and the applicable national regulations, the patient provided written informed consent, and the study was approved by our Institutional Ethical Committee (ID 4858).

Consent for publication

The patient provided informed consent for publication.

Author contributions

Alberto Fresa: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

Idanna Innocenti: Conceptualization; Project administration; Supervision; Writing - review & editing.

Annamaria Tomasso: Conceptualization; Writing – review & editing.

Luca Stirparo: Conceptualization; Writing – review & editing.

Antonio Mosca: Conceptualization; Writing – review & editing.

Francesco Iadevaia: Conceptualization; Writing – review & editing.

Francesco Autore: Conceptualization; Project administration; Supervision; Writing – review & editing.

Luca Laurenti: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data and materials are available upon request.

ORCID iDs

Alberto Fresa https://orcid.org/0000-0002-8084-9009

Annamaria Tomasso https://orcid.org/0009-0005-5361-7463

Supplemental material

Supplemental material for this article is available online.

References

1. Autore F, Pasquale R, Innocenti I, et al. Autoimmune hemolytic anemia in chronic lymphocytic leukemia: a comprehensive review. *Cancers (Basel)* 2021; 13(22): 5804.
2. Gurnari C and Maciejewski JP. How I manage acquired pure red cell aplasia in adults. *Blood* 2021; 137: 2001–2009.
3. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *BMJ Case Rep* 2013; 2013: bcr2013201554.
4. D'Arena G, Vigliotti ML, Dell'Olio M, et al. Rituximab to treat chronic lymphoproliferative disorder-associated pure red cell aplasia. *Eur J Haematol* 2009; 82(3): 235–239.
5. Vitale C, Salvetti C, Griggio V, et al. Preexisting and treatment-emergent autoimmune cytopenias in patients with CLL treated with targeted drugs. *Blood* 2021; 137: 3507–3517.
6. Nikitin E, Kislova M, Morozov D, et al. Ibrutinib in combination with rituximab is highly effective in treatment of chronic lymphocytic leukemia patients with steroid refractory and relapsed autoimmune cytopenias. *Leukemia* 2023; 37(7): 1464–1473.
7. Lechner KS, Neurath MF and Weigmann B. Role of the IL-2 inducible tyrosine kinase ITK and its inhibitors in disease pathogenesis. *J Mol Med (Berl)* 2020; 98(10): 1385–1395.