Case Reports in Oncology

Case Rep Oncol 2024;17:69–74
DOI: 10.1159/000535636
Received: March 15, 2023
Accepted: November 29, 2023
Published online: January 9, 2024

Case Report

Unusual Presentation of B-Cell Chronic Lymphocytic Leukemia Accompanied by Pure Red Cell Aplasia: Case Report

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Keywords
Chronic lymphocytic leukemia · Pure red cell aplasia · Anemia · Case report

Abstract
Introduction: Pure red cell aplasia (PRCA) is a rare bone marrow failure characterized by normocytic anemia and severe reticulocytopenia. ***Case Presentation:*** We describe the case of a 38-year-old female who presented with severe anemia. Further investigation revealed the etiology of anemia to be PRCA. She was subsequently diagnosed with chronic lymphocytic leukemia (CLL) B-cell type on bone marrow biopsy. The patient refused blood transfusion support. She failed to improve and expired despite treatment with rituximab and steroids. ***Conclusion:*** Our case is an unusual presentation of PRCA that led to the diagnosis of CLL. PRCA is an extremely rare cause of anemia in CLL, occurring in around 1% of patients. The pathogenesis is thought to be immune mediated. Treatment of PRCA in CLL involves immunosuppressive therapy with steroids, cyclosporine, and rituximab, yet it is usually refractory in most cases.

Introduction

Pure red cell aplasia (PRCA), initially described in 1922, is a rare bone marrow failure defined by normocytic normochromic anemia and severe reticulocytopenia. It is characterized by marked reduction or absence of erythroid precursors, with normal production of megakaryocyte and white cell precursors. It is associated with various conditions such as

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thymoma, autoimmune disorders, lymphoproliferative, myeloproliferative diseases, and infections, particularly human parvovirus B19 [1]. Chronic lymphocytic leukemia (CLL) is among the lymphoproliferative disorders associated with PRCA [2]. Important causes of anemia in CLL are autoimmune hemolysis or, in advanced stages of CLL, bone marrow failure secondary to tumor cell infiltration [3]. The prevalence of PRCA in patients with CLL is rare, estimated around 1% [4]. The pathophysiology behind PRCA in hematological disorders is not yet known. The process is believed to entail a cellular and humoral-mediated immune response by the tumor on erythroid progenitors [5]. Despite the use of immunosuppressive and biologic agents including rituximab, PRCA in CLL tends to be refractory to treatment, with high rates of relapse and poor long-term prognosis. We report a case of a young female patient who presented with PRCA and was found to have B-cell CLL. This case helps increase clinicians' awareness of PRCA as an atypical manifestation of lymphoproliferative disorders, its diagnosis, and management. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535636).

Case Description

A 38-year-old African American female identifying as Jehovah's witness, presented with complaints of fatigue and generalized weakness for the past 2 months, worsening over a 3-day period. She had a medical history of discoid lupus, iron deficiency anemia, sickle cell trait, prediabetes, schizophrenia, and a recent emergency visit to an outside hospital for acute psychosis.

On physical examination, the patient was hypotensive with a blood pressure of 89/47 mm Hg and a pulse rate of 97 beats per minute. She appeared weak and cachectic, had bitemporal hair thinning, pale and dry oral mucosa, and hyperpigmented facial scars. Lymphadenopathy and hepatosplenomegaly were not observed on the physical exam. Laboratory studies on admission are shown in Table 1. White blood cells and platelet counts were normal, but normocytic normochromic anemia was seen. Peripheral blood smear showed marked red blood cell anisopoikilocytosis, hypochromia, and significant agglutination with multiple rouleaux formation. There was no evidence of hemolysis. Schistocytes and nucleated RBCs were absent. The morphology of polymorphonuclear cells and platelets was normal.

She was admitted for severe symptomatic anemia with profound reticulocytopenia suspicious of PRCA aplasia. She refused blood transfusion in accordance with her religious beliefs. Patient was started on daily 200 mg intravenous iron injections, in addition to erythropoietin 40,000 units twice daily. Daily prednisone 1 mg/kg body weight was administered due to the likelihood of an underlying autoimmune process. Further workup revealed hypergammaglobulinemia 30.6% on protein electrophoresis. Serum immunofixation showed a biclonal immunoglobulin G (IgG) protein with kappa specificity.

Bone marrow aspiration and biopsy, shown in Figure 1, demonstrated characteristic findings of marked erythroid hypoplasia. There was a small population, shown in Figure 2, representing 2.5–5% of total cells, of monoclonal kappa B cells (CD19+, CD20+, CD22+ co-expressing CD5, and CD23). The immunophenotype was consistent with a clone of CLL. Based on these findings, the patient was diagnosed with acquired PRCA secondary to B-CLL. The immunohistochemistry of B19 parvovirus was negative. Staging computed tomography of the chest, abdomen, and pelvis identified a prominent left axillary lymph node measuring 1.4 cm. She was treated with rituximab (infusion of 540 mg/m^2).

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Table 1. Laboratory data

Variable		Reference range	
White cell count	8.6	4.0–10.0	10^3/μL
Neutrophils	52.8	34.0–71.1	%
Lymphocytes	36.4	19.3–51.7	%
Monocytes	9.2	4.7–12.5	%
Red blood cells	0.94	3.93–5.22	10^6/μL
Hemoglobin	2.6	11.2–15.7	gm/dL
Hematocrit	7.5	34.1–44.9	%
Mean corpuscular volume	79.8	79.4–94.8	fL
Mean corpuscular hemoglobin concentration	34.7	32.2–35.5	gm/dL
Platelets	323	150–450	10^3/μL
Reticulocyte	0.05	0.50–1.70	%
Retic absolute	0.0005	0.0164–0.0776	10^6/μL
Biochemical		**Reference range**	
Total bilirubin	0.4	0.1–1.2	mg/dL
Serum iron	208	50–170	μg/dL
Ferritin	177.0	12.0–150.0	ng/mL
Total iron binding capacity	246.4	250–400	μg/dL
Iron saturation	84.4	20–55	%
Lactate dehydrogenase	186	100–190	IU/L
Haptoglobin	66	34–200	mg/dL
Vitamin B12	749	160–950	pg/mL
Cold agglutinin titer	Negative		

Eleven days after hospitalization, patient's hemoglobin levels remained low at 0.8–1.9 gm/dL, with normal white blood cell and platelet counts. She deteriorated rapidly after an episode of profuse vomiting that led to a cardiac arrest. Cardiopulmonary resuscitation attempts failed, and she subsequently expired.

Discussion

PRCA was first described in 1922 by the absence of erythroid precursors in the bone marrow with normal megakaryocytes and white cell precursors. Chronic PRCA can be congenital, such as Diamond-Blackfan syndrome in children, or acquired in adults with thymoma, hematological malignancies, and immunosuppression, such as HIV. Certain viral infections, most notably parvovirus B19, induce an acute form of PRCA. There are reports of a chronic form of PRCA associated with persistent parvovirus B19 infection, especially in immunosuppressed states [1]. PRCA is known to occur with some chemotherapeutic agents and resolves upon withdrawal of the implicated drug [2]. This patient had an acquired chronic form of PRCA attributed to CLL.

Common causes of anemia in CLL include autoimmune hemolytic anemia (AIHA), hypersplenism, and leukemic cell infiltration of normal marrow, leading to marrow failure [3]. The anemia in CLL is rarely attributed to PRCA. While 7–10% of CLL patients develop

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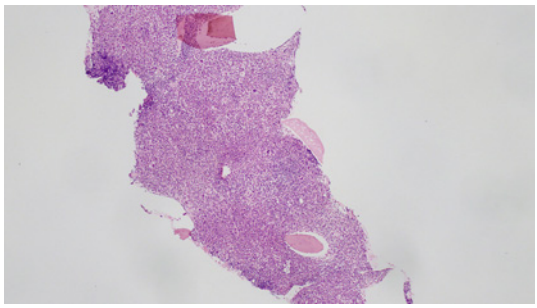

Fig. 1. Bone marrow biopsy showing markedly decreased erythropoiesis (low power magnification, ×10, H&E stain).

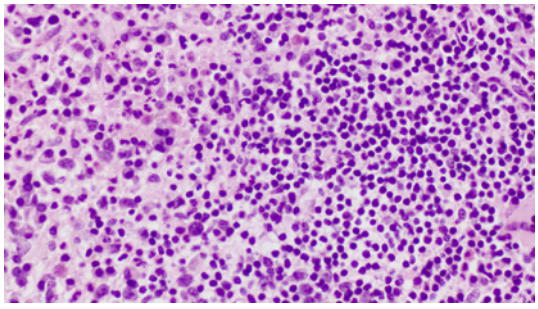

Fig. 2. Bone marrow biopsy with interstitial aggregates of well-differentiated lymphocytes, immunoreactive to CD5+, CD20+, PAX5+, and negative for cyclin D1, comprising approximately 2.5–5% of marrow cellularity (high power magnification, ×40, H&E stain).

AIHA, less than 1% present with PRCA [4]. Patients with the latter usually have a severe transfusion-dependent anemia, requiring one to two packed red cell units a week. A bone marrow biopsy must be performed in all CLL patients with an unexplained degree of anemia [6]. Main criteria used to diagnose CLL-associated PRCA include severe anemia, reticulocytopenia, ≤1% of erythroid precursors in the bone marrow, absence of parvovirus B19 infection by polymerase chain reaction, absence of hemolysis, direct antiglobulin test negativity, and an onset of 4 weeks from the last chemotherapy infusion [6]. Furthermore, PRCA may occur before, during, or after the diagnosis of CLL [6].

In this patient, the normocytic normochromic anemia associated with reticulocytopenia, in the presence of normal white cell and platelet counts raised concern for PRCA. The final diagnosis was established with the bone marrow biopsy showing hypercellular marrow with CLL involvement and marked red cell hypoplasia. E-cadherin and CD71 staining yielded few scattered erythroid elements. In CLL, PRCA can be seen with other autoimmune cytopenia like AIHA, making the diagnosis challenging [7]. AIHA was ruled out by the presence of normal bilirubin, haptoglobin, and lactate dehydrogenase levels, with the absence of hemolysis on peripheral blood smear. B12 and iron studies were replete. The involvement of parvovirus B19 was definitively excluded with the negative immunohistochemistry result for the virus in the bone marrow. There was no evidence of hepatitis infection. To minimize blood draws, some tests from the viral panel, such as Epstein-Barr virus and HIV, were not checked.

The mechanism behind the pathogenesis of PRCA in CLL is not well understood. It is believed that T-lymphocyte dysregulation has an inhibitory effect on the growth of erythroid progenitors, either through a direct cytotoxic T-cell-mediated attack or via cytotoxic T-cell proapoptotic cytokine production. Other cases of PRCA are presumed to be mediated by natural killer cells directly lysing erythroblast. Inhibition of erythroid lineage by benign or clonal B-lymphocyte autoantibody production is another postulated mechanism [4].

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The clinical outcome of PRCA depends on the underlying cause and treatment. Multiple regimens have been proposed for the treatment of PRCA over the years. Acquired PRCA is usually refractory to conventional treatment with steroids commonly employed in acute PRCA. This is especially true for PRCA secondary to CLL. Prednisone at a dose of 1–1.5 mg/kg/day is frequently used as the first agent in CLL patients with PRCA [8]. The use of immunosuppressive therapy such as azathioprine, cyclophosphamide, and cyclosporine-A has been adapted in steroid-refractory cases [2]. Biologics such as rituximab, alemtuzumab, and antithymocyte globulin have also been reported [9]. Rituximab, described in several cases, has proven efficacy and shown success in CLL-related PRCA [10]. Limited reports addressed treating autoimmune cytopenia in CLL patients with ibrutinib [11]. Higher-quality evidence is lacking to generate definite treatment recommendations. Our index patient did not respond to corticosteroids. The salvage use of Rituximab in her case was limited to one dose and did not show any benefit.

We have described a rare occurrence of PRCA in a newly diagnosed CLL patient. PRCA is a debilitating autoimmune sequela of CLL. PRCA, at any time, can complicate the course of CLL, thus posing both diagnostic and therapeutic challenges. Our index patient had a unique presentation found only in a few other reported cases in the literature, reminding our readers of the possibility of lymphoproliferative disease in patients presenting with PRCA. Diagnosis is established from the clinical presentation, blood analysis, and bone marrow examination. Further molecular studies are needed to understand the mechanisms underlying CLL-associated PRCA. Immunosuppressant and biologic agents are the mainstay treatment, with the goal of restoring erythropoiesis and evading the need for blood transfusion. Optimal treatment regimens for such cases are still lacking.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient prior to expiration for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors report no conflicts of interest.

Funding Sources

The authors received no financial support for this study.

Author Contributions

Jane Atallah wrote the initial draft and revised the manuscript. Yarub Al Alousi wrote the initial draft of the manuscript. Nehemias Guevara contributed to the interpretation of the data. Iurii Statnii was involved in the management of the patient. Sameh Nassar was involved in the management of the patient. Ivette Vigoda supervised all phases of writing. All authors have read and approved of the manuscript for submission.

Data Availability Statement

The research data behind this study are not publicly available due to legal and ethical concerns. Upon reasonable request, the clinical data can be made available through the corresponding author by access to St. Barnabas Hospital Health System electronic medical records.

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