Case Report

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Pure red cell aplasia in chronic lymphocytic leukemia: Case report and review of literature

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Abstract:

Despite being immune deficient, chronic lymphocytic leukemia (CLL) patients have an increased incidence of autoimmune cytopenias secondary to autoantibody formation. These are: warm autoimmune hemolytic anemia; idiopathic thrombocytopenia; pure red cell aplasia (PRCA), and In this case report, we describe a patient with CLL who developed severe anemia requiring frequent red cell transfusion after the third cycle of chemotherapy. Blood film showed no evidence of hemolysis and absolute reticulocytopenia. Bone marrow showed erythroid hypoplasia and residual interstitial infiltrate of CLL. The diagnosis of CLL-induced PRCA was made, and the patient showed a prompt and dramatic response to treatment with cyclosporine.

Key words:

Chronic lymphocytic leukemia, pure red cell aplasia, literature review

Case Report

A 65-year-old male, previously healthy was referred from another health-care facility on October 23, 2015, because of high total white cell count with 1 month history of fatigue and painless cervical lymphadenopathy. On examination, he was not pale not jaundice, not tachypneic. There is generalized lymphadenopathy (bilateral tonsillar, left supraclavicular, and bilateral axillary nodes). Vital signs include blood pressure 130/80, temperature 37.2°C, and pulse rate 88/min. cardiorespiratory examination was unremarkable. Abdominal examination showed no tenderness, no mass, and splenomegaly was felt 10 cm below the left costal margin.

Complete blood count (CBC) was as follows: Hemoglobin (Hb) 12.7 g/dL, white cell count 77.5×10^9/L, and platelet count 90×10^9/L. Blood film showed absolute lymphocytosis many small mature lymphocytes with many smudge cells are seen suggestive of chronic lymphocytic leukemia (CLL). Bone marrow study revealed hypercellular marrow with infiltration by small mature lymphocytes constituting 90% of all nucleated cells. The picture goes with lymphoproliferative disorder and immunophenotyping is recommended to confirm the diagnosis of CLL.

The patient had been further investigated outside the country on November 2015, and flow cytometry on peripheral blood was done, which was reported as CD20+ B-cell CLL. Chest X-ray showed possible mass as in Figure 1. Whole body positron imaging tomography-computed tomography was done and findings are seen in Figure 2. Staging workup revealed Binet stage C/Rai stage IV. He was started on chemotherapy with the bendamustine + rituximab (BR) regimen [Figure 3] together with uricosuric drugs and hydration and received his first cycle on November 23, 2015. He showed good improvement to the first cycle of chemotherapy with rapid reduction in the size of the nodes, splenic size, and total white cell count and advised to receive the second cycle in Iraq on December 24, 2015. In our department, the chemotherapy regimen was changed to fludarabine, cyclophosphamide, and rituximab (FCR) regimen [Figure 3] because of unavailability of bendamustine in our facility and received the first cycle of FCR in the scheduled date.

On February 2016, the patient presented with progressive pallor and shortness of breath. CBC revealed white blood cell (WBC) 3.7×10^9/L, Hb 5.5 g/dL, and platelets 50×10^9/L. Reticulocyte count was 1%, and direct antiglobulin test (DAT) was negative.

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Then the patient was admitted to the hematology ward of Merjan Teaching Hospital on frequent intervals to receive red cell transfusion, but the Hb level failed to rise appropriately after transfusion. This was attributed first to the bone marrow failure from the effects of chemotherapy, hence, bone marrow aspiration and biopsy after the third cycle of FCR was done revealed hypercellular with diffuse lymphoid cells infiltrate, and the patient is not in remission. At this point, a plan is made to change the chemotherapy regimen to BR again, and the first cycle was given on March 30, 2016. However, anemia persisted, and the patient was re-evaluated again on May 2016, and the CBC was as follows: WBCs 4.5 × 10^9/L, Hb 6.1 g/dL, and platelets 69 × 10^9/L. Absolute reticulocyte count was <0.03%. DAT was negative. Bone marrow aspiration was cellular with erythroid hypoplasia and few erythroblasts and bone marrow biopsy was hypocellular for the patient's age with preserved architecture with many granulocytic precursors' adequate megakaryocytes and few erythroid precursors with little nodular mature lymphoid cell infiltration [Figure 4].

The final diagnosis was CLL not in remission with pure red cell aplasia (PRCA). Epstein–Barr virus (EBV) and cytomegalovirus (CMV) viral titers are within the reference ranges (EBV 0.14 IU/mL IgM (reference

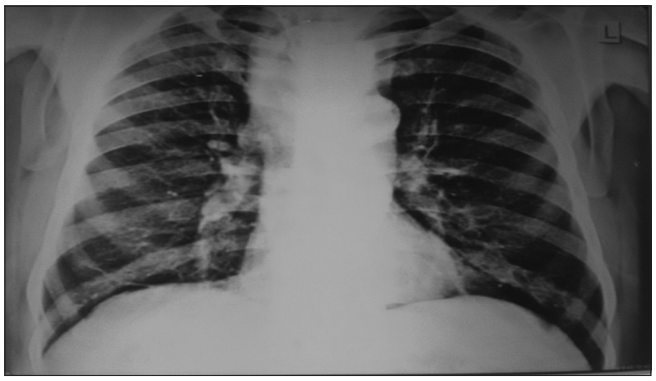

Figure 1: Chest X-ray with deviation of the mediastinum to the right suggesting left superior mediastinal mass

BR (Bendamustine + Rituximab)

Drug	Dose	Method	Day
Bendamustine	200 mg	IV (30 min)	D1-2
Rituximab	900 mg	IV (2 hr)	D1

First Cycle – November , 23 , 2015

Second Cycle – May , 30 , 2016

Third Cycle – April , 27 , 2016

4th Cycle – May , 15 , 2016

5th Cycle- July , 24 , 2016

6th Cycle – August , 22 , 2016

FCR (Rituximab ,Fludarabine , cyclophosphamide)

Drug	Dose	Method	Time
Rituximab	900 mg d1 cycle 1 and 1000 mg d1 cycle 2-6	IV	D1
Fludarabine	50 mg	i.v (30min inf)	D1-3
Cyclophosphamide	500 mg	i.v (1h inf)	D1-3

First Cycle – Dec , 21 , 2015

Second Cycle – Jan , 17 , 2016

Third Cycle – Feb, 14 , 2016

Figure 3: Chemotherapy regimen schedule

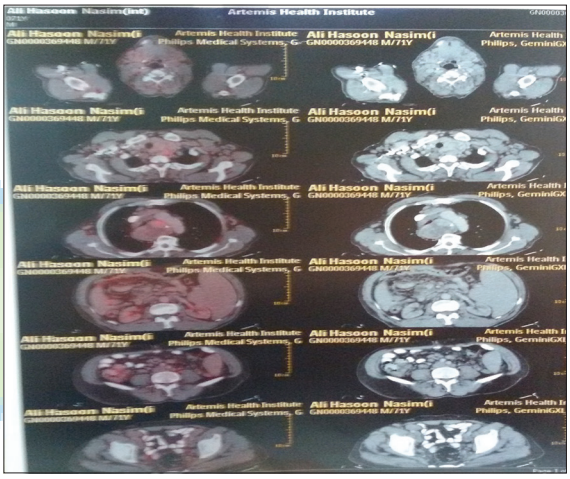

Figure 2: Whole body positron imaging tomography-computed tomography reveals splenomegaly with multiple enlarged faintly avid fludeoxyglucose avid cervical, axillary, mediastinal, retroperitoneal, pelvic and inguinal lymph nodes. There is also large heterogeneously enhancing multinodular left lobe of thyroid, extending into the mediastinum in the retro tracheal space, displacing the trachea to the right, reaching almost up to the level of the carina

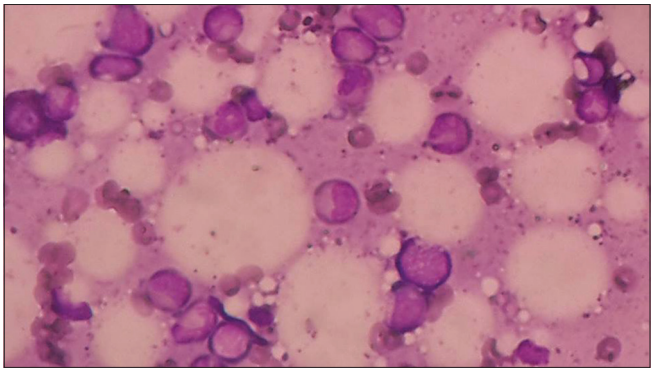

Figure 4: Bone marrow study of the patient. Bone marrow aspiration was hypocellular for the patient's age with preserved architecture with many granulocytic precursors, adequate megakaryocytes, and few erythroid precursors with few nodular mature lymphoid cell infiltrations. The final diagnosis was chronic lymphocytic leukemia not in remission with pure red cell aplasia

range: Negative <0.6), 0.1 IU/mL IgG (reference range: Negative <0.8); CMV 0.05 IU/mL IgM (reference range: Negative <2.0) 0.7 IU/mL IgG (reference range: Negative <2.0). Polymerase chain reaction for parvovirus B19 was unavailable in our facility.

Based on these findings, the patient was started on cyclosporine A (Neoral, Novartis)® 5 mg/kg/day in two divided doses with monitoring of renal, liver function, and serum electrolytes and the patient continued on BR regimen in the scheduled dates.

Follow-up CBC done in June 2016 was as follows: WBCs 3.7×10^9/L, Hb 8.6 g/dL and platelets 50×10^9/L. Reticulocyte count was 10%, and the patient became transfusion-independent. Serial follow-up CBC was shown in Table 1.

After finishing chemotherapy in August 2016, the patient was evaluated for remission. CBC: WBCs 1.1×10^9/L, Hb 11.4 g/dL, and platelets 83×10^9/L. Bone marrow study showed hypocellular marrow with active erythropoiesis and normoblastic maturation, and the patient was in complete remission (CR) [Figure 5].

The patient was well when seen in the next monthly visit with CBC showed WBCs 1.7×10^9/L, Hb 11.9 g/dL, and platelets 107×10^9/L. Reticulocyte count was 3%. Renal, liver function, and serum electrolytes were normal, and serum cyclosporine was in the therapeutic range.

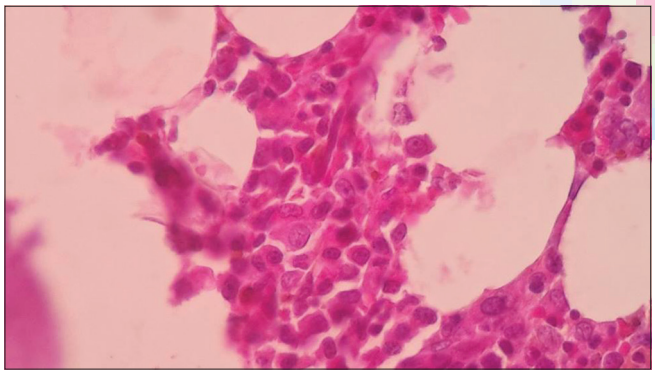

Figure 5: Bone marrow study showed hypocellular marrow with active erythropoiesis and normoblastic maturation and the patient was in complete remission

Discussion

CLL is a malignancy of mature B cells characterized by lymphocytosis, lymphadenopathy, splenomegaly, and cytopenias. It is a disease of the elderly with a median age at diagnosis of 72 years.[1] 70%–80% of patients are diagnosed incidentally when they have a routine blood count. Alternatively, lymphadenopathy, splenomegaly, or both may be detected during a regular physical examination. When symptomatic, the most frequent complaint is fatigue or a vague sense of being unwell. Less frequently, enlarged nodes or the development of an infection is the initial complaint. Fever and weight loss are uncommon at presentation but may occur with the advanced and drug-resistant disease.[2] The diagnosis of CLL The diagnosis of CLL, as defined by the IWCLL 2008 criteria, which requires an absolute malignant B-cell lymphocyte count of >5000/μL which made by the identification of the cells bearing the unique phenotype of CLL using immunophenotyping panel on peripheral blood.[3,4]

Autoimmune complication of chronic lymphocytic leukemia

CLL is generally characterized by profound immunosuppression and hypogammaglobulinemia and, as a consequence, patients are subject to a high rate of infections.[5] Despite being immune deficient, CLL patients have an increased incidence of autoimmune cytopenias (AIC) secondary to autoantibody formation. These include autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), PRCA, and autoimmune granulocytopenia.[6,7]

These disorders are caused by the immune dysregulation in CLL, may be triggered by chemotherapy, and are treated with immunosuppressive.[2] Autoantibodies responsible for the autoimmune manifestations in CLL are not produced by the leukemic clone and are polyclonal.[6] The immune cytopenias may be present before or at the time of diagnosis in one-third and during disease in two-thirds.[5,7]

Pure red cell aplasia

PRCA whether congenital (Blackfan–Diamond syndrome) or acquired (autoimmune disorders, lymphoproliferative disorders (B- and T-lymphoma, Hodgkin disease, CLL), myeloproliferative disorders, acute and chronic hepatitis, thymoma, and with drug-induced and other infections, particularly viruses such as human parvovirus B19) is a rare bone marrow failure syndrome characterized by progressive normocytic anemia and reticulocytopenia but normal myeloid

Table 1: Complete blood count during the course of the treatment and after treatment of pure red cell aplasia

Date	WBC (10^9/L)	Hb (g/dL)	Retic count (%)	Platelets (10^9/L)
October 23, 2015	77.5	12.7		90
November 30, 2015	14.9	11.7		151
February 17, 2016	3.7	5.5	1	50
March 03, 2015	2.5	6.5		103
May 15, 2016	4.5	6.1	<0.03	69
June 21, 2016	2.8	8.6	10	78
August 07, 2016	1.1	11.4	5	83
August 16, 2016	2.9	11.6	3	65
August 25, 2016	2.8	11.9	3	107
October 24, 2016	1.7	11.9	3	107

Hb = Hemoglobin, WBC = White blood cell

and megakaryocytic cell lineages.[8] It characterized by the disappearance of red cell precursors from the bone marrow and a profound reduction in the absolute reticulocyte count.[4]

Most studies have suggested that PRCA is a rare complication of CLL, occurring in approximately 0.5% of patients. However, if this disorder is specifically sought with a bone marrow aspiration and absolute reticulocyte count, PRCA may be found in up to 6% of patients with CLL.[9] Unlike other autoimmune complications of CLL which are B-cell mediated, PRCA is a T cell–dependent complication and occurs relatively early in the course of the disease.[4] The etiology of disease-related PRCA is believed to be related to the cytotoxic effect of a T-cell large granular lymphoma clone on erythroid progenitor cells. These CD3-, CD8-, and CD57-positive coexpressing cells slowly accumulate in the marrow of patients with PRCA. Occasional cases have been observed after parvovirus B19 infection.[1,10]

Differential diagnosis

Anemia due to bone marrow infiltration by malignant lymphocytes suppressing erythropoiesis or secondary to chemotherapy is the most frequent cause of anemia in CLL. Red blood cell production failure due to parvovirus B19 infection must be excluded by polymerase chain reaction-based tests for viral acids. Moreover, AIHA may complicate CLL in approximately 5%–37% of patients with a higher incidence in advanced disease. Reticulocytosis, increased indirect bilirubin and lactate dehydrogenase serum level, low haptoglobin serum level, and DAT positivity are the main laboratory features. Myelodysplastic evolution due to previously given therapy must also be taken into account.[8]

Management

The primary goal in PRCA is to induce the recovery of erythropoiesis avoiding an excess of transfusions. Several treatment regimens usually effective in autoimmune conditions fail in secondary PRCA, especially when this condition is associated to CLL or lymphoma.[5] Transfusion of packed red cells is usually indicated in patients who are clinically symptomatic from severe anemia.[1] Previous reports that corticosteroid therapy at a dose of 1 mg/kg/day of prednisone is the first line of treatment.[8] However, steroids generally poorly responsive to CLL-induced PRCA[5] and more than 80% of patients relapsed within 24 months after remission and tapering steroids and only 11% continue to be in remission after 5 years.[8] Oral cyclosporine is the treatment of choice[5] it works by inducing a depletion of T-cells, strongly support the immunologically-mediated nature of the disease due to the direct T-lymphocytes cytotoxic effect on erythroid progenitors.[8]

The majority of patients with CLL and PRCA will have a complete response to treatment with oral cyclosporine. The usual dose is 10–14 mg/kg/day in two divided doses, with adjustment according to trough serum levels, response, and tolerance. In particular, renal and hepatic function and serum magnesium levels need to be closely monitored. In a series of 31 patients with CLL, oral cyclosporine (300 mg daily) resulted in responses in over 60% of patients. Mild reversible nephrotoxicity may warrant dose adjustment in some patients.[4,11] Cyclosporine should be continued for approximately 3 months if there is a response; slow tapering is then instituted as relapse is common when this medication is discontinued.[12] Most patients exhibit a response by having reticulocytosis within the first 2–3 weeks from start of therapy, but substantial response may occur up to months.[5,13] There are several case reports of successful treatment of patients with PRCA with anti-CD20 monoclonal antibody rituximab as a single agent but the response rate is lower than for AIHA or ITP[14,15] it acts by depleting B-cells by means of several mechanisms: Antibody-dependent cell mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and apoptosis[8] but the mechanism of action of rituximab in PRCA is not entirely clear. The rapid response that has been observed in some patients raises the possibility of mechanisms different from those thought to be active in other AIC.[5] It is also effective in controlling CLL itself; thus, its efficacy may be related to its anti-tumor properties.[8] The dose is (375 mg/m^2/week for 8 weeks).[14] Parvovirus can cause PRCA in CLL[4] Intravenous immunoglobulin have been reported to be effective in some cases of PRCA associated to parvovirus B19 infection because they contain neutralizing antibodies against the virus.[16,17] Alemtuzumab is a humanized monoclonal antibody that recognizes the CD52 antigen expressed on T- and B-lymphocytes. Similar to rituximab, alemtuzumab kills the target cells by ADCC, CDC, and apoptosis and is effective against CLL itself by its anti-tumor properties[5,8] Rossignol *et al*. recently reported the efficacy of rituximab-cyclophosphamide-dexamethasone combination in five PRCA patients. All five patients obtained CR and only one patient relapsed.[18]

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Conflicts of interest

There are no conflicts of interest.

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