LGLL is a lymphoproliferative disorder that is known to be associated with autoimmune conditions, such as rheumatoid arthritis and Sjogren's syndrome. To our knowledge, it has only been reported once in association with AHA. This case would be the second of such report of LGLL as a potential cause of AHA [2]. While our predecessors managed bleeding using bypassing agents, our choice varied based on the patient's age and comorbidities [2].

Hemostasis in AHA can be achieved by administering FVIII bypassing agents in the form of recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC) which can generate thrombin in a non-physiologic fashion, independent of FVIII. A practical limitation of these products is that their activity cannot be monitored with standard coagulation assays and they carry an increased risk of thrombosis, particularly in older individuals with vascular co-morbidities. Recombinant porcine FVIII (rPorcine FVIII) is an alternative hemostatic agent for AHA since it is quite different from human FVIII and is not recognized by the autoantibody in most cases, thus allowing the coagulation cascade to proceed in a normal physiologic fashion. An advantage of this is that it can be measured by checking FVIII activity, thereby allowing it to be measured to maintain an activity that minimizes the risk of both bleeding due to sub-therapeutic levels and thrombosis from supra-therapeutic levels. Due to this, we prefer rPorcine FVIII over bypassing agents especially in older patients with cardiovascular comorbidities [3]. While there are no head-to-head comparison studies between the two, the decision is usually based on the availability, prior case-to-case experience, and economic considerations.

Immunosuppressive therapy (IST) is recommended in all adults with AHA to achieve FVIII inhibitor eradication as the bleeding-related morbidity and mortality is substantial. In multiple studies and meta-analyses, it was found that combination IST (corticosteroids, cyclophosphamide, and rituximab) was superior to corticosteroids alone [3].

Our patient had LGLL as a potential underlying trigger for the development of AHA. Usually, this is an indolent neoplasm not requiring specific management other than watchful observation. However, concurrence with AHA and the patient's age necessitated chemotherapy with cyclophosphamide. Other instances where LGLL requires treatment are severe neutropenia (absolute neutrophil count or ANC $<0.5\times10^9$/L), moderate neutropenia (ANC $>0.5\times10^9$/L) with superinfections, autoimmune conditions needing treatment, and transfusion-dependent anemia [5].

In summary, our case is the second report in the literature on AHA occurring in association with LGLL. Also, the discussion of our therapeutic choice for hemostasis presents nuances in the management of AHA in the elderly and those with cardiovascular comorbidities.

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Department of Internal Medicine, [1]Byramjee Jeejeebhoy Medical College, [2]Jagtap Clinic and Research Center, Pune, [3]Bangalore Medical College and Research Institute, Bangalore, India, [4]James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA

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An illustrative case of B-cell prolymphocytic leukemia

TO THE EDITOR: B-cell prolymphocytic leukemia (B-PLL) is an extremely rare malignancy ($<$1% of B-cell leukemias) [1, 2]. Given a wide array of differential diagnoses, establishing the correct diagnosis is challenging [3]. Histomorphological evaluation of the peripheral blood (PB) smear and diligent interpretation of the immunophenotype of lymphocytes by an expert pathologist are essential for the diagnosis of B-PLL. In this report, we describe the case of a patient with B-PLL, discuss the diagnostic possibilities, and briefly review the relevant literature.

A 65-year-old man presented to our hospital in August 2019 with the complaints of fever and left upper abdomen pain for 6 months. General examination showed pallor.

Abdomen examination revealed massive splenomegaly (12 cm below left costal margin). CT scan of the abdomen showed splenomegaly (23 cm), and multiple enlarged lymph nodes in the retroperitoneal, peri-portal, peri-epigastric, and pelvic areas. Complete blood count results showed hemoglobin level to be 70 g/L and white cell count at 470×10^9/L (including 99% lymphocytes and platelet count of 127×10^9/L). Peripheral blood (PB) smear revealed 90% prolymphocytes (Fig. 1). Immunophenotypically, the lymphocytes were CD45$^+$, CD5$^+$, CD23$^+$ (heterogeneous), CD200^{dim+}, CD19$^+$, CD20$^+$ (bright), surface CD22$^+$ (bright), surface CD79b$^+$ (bright), CD38$^+$, surface kappa$^+$ (bright), and surface IgD^{dim+}. Lymphocytes were negative for CD10, FMC7, CD25, CD11c, CD123, CD103, surface lambda, Immunoglobulin G (IgG), and Immunoglobulin M (IgM) (Fig. 2). Morphological and immunophenotypic findings were consistent with the diagnosis of de-novo B-PLL. PB interphase fluorescent in-situ hybridization (FISH) failed to reveal deletion 11q, deletion 6q, deletion 17p, trisomy 12, deletion 13q, and t (11,14) (q13; q32). Bone marrow (BM) biopsy was hypercellular, and showed complete replacement by prolymphocytes. Immunohistochemistry for cyclin D1 on BM biopsy was negative. Cytogenetic analysis of BM aspirate revealed a normal karyotype. Iron profile, serum vitamin B12, and folate levels were normal. Viral markers and direct antiglobulin test were negative. Serum lactate dehydrogenase was elevated (784 U/L; normal, <250 U/L). The patient was treated with BR chemoimmunotherapy [Bendamustine (90 mg/m^2 on days 1 and 2) and Rituximab (375 mg/m^2 on day-1)] administered every 28 d. Patient achieved complete remission (CR) after 6 cycles of BR, and continues to be in CR till date.

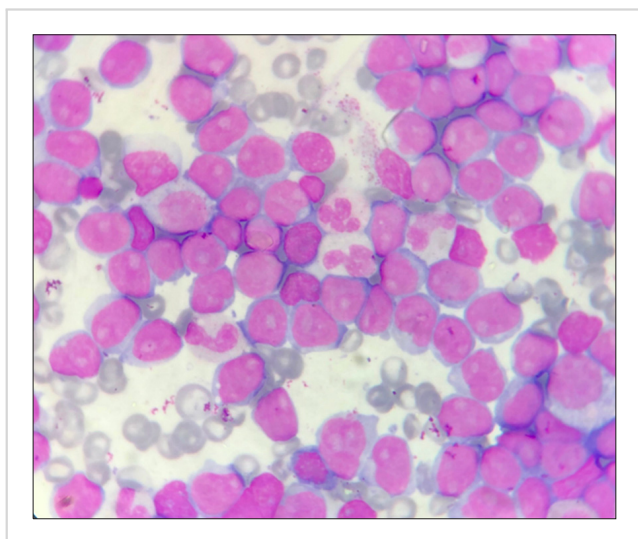PLL is defined as the presence of >55% prolymphocytes

Fig. 1. Microphotograph of the bone marrow aspirate smear showing almost complete replacement by prolymphocytes (2–2.5 times the size of a mature lymphocyte with mild-moderate cytoplasm, open chromatin, and prominent nucleoli, Giemsa–Wright stain, ×100).

in the PB and BM. PLL has two subtype: T-PLL and B-PLL, the latter being much rarer [1-3]. Immunophenotypically, B-PLL shows bright expression of B-cell markers (CD19, CD20, FMC7) and surface immunoglobulins (sIg), negative expression of CD5, CD23, CD200, CD10, and T-cell markers, and demonstrates a low Matutes score [3]. Expression of CD5 and CD23 is uncommon (1/3rd cases) in B-PLL [1], and CD200 expression has occasionally been reported [4]. B-PLL could arise either de-novo or from prolymphocytic transformation of chronic lymphocytic leukemia (CLL). In cases of prolymphocytic transformation of CLL, prolymphocytes retain the immunophenotype of CLL, though they show a brighter sIg expression [1]. Old age (6th–7th decade), B-symptoms, massive splenomegaly, high white cell count, and anemia with/without thrombocytopenia are the classical clinical features of B-PLL. Peripheral lymphadenopathy is uncommon [2]. Cytogenetic abnormalities, c-myc aberration, and deletion 17p/TP53 mutation are seen in about 75%, 60%, and 40% cases, respectively [5]. Based on the c-myc aberration, and deletion 17/TP53 mutation, B-PLL is classified into three prognostic groups; low-risk (myc-activation- and deletion 17p$^-$), intermediate-risk (myc-activation$^+$ and deletion 17p$^-$), and high-risk (myc-activation$^+$ and deletion 17p$^+$) [6]. Clinical course of B-PLL is aggressive. Prognosis is poor with median overall survival of about 2–3 years [2]. Due to its rarity and absence of prospective clinical trials, there are no formal guidelines for the management of B-PLL. Consensus regarding the treatment of B-PLL is mainly derived from anecdotal reports, and case series [7]. Patients with deletion 17p/TP53 mutations require targeted therapies like Bruton tyrosine kinase inhibitors (Ibrutinib), phosphoinositide 3-kinase inhibitors (idelalisib), and alemtuzumab (anti-CD52 monoclonal antibody). Patients without deletion 17p/TP53 mutations might benefit from chemo-immunotherapies (rituximab-based combinations with fludarabine or bendamustine). Allogeneic stem cell transplant should be considered either frontline in young and fit patients—particularly those with deletion 17p/TP53 mutations—or in relapsed/refractory cases [7-9]. Strong expression of B-cell markers, and surface kappa, heterogeneous CD23, and dim CD200 were against the diagnosis of CLL in our case. Presence of prolymphocytes, and negative expression of CD10 excluded follicular lymphoma. Lack of CD25/CD11c/CD123/CD103 ruled out hairy cell leukemia. Presence of classical prolymphocytes in our case did not support the diagnosis of marginal zone lymphoma, which usually shows the presence of villous lymphocytes on PB and BM. Negative interphase FISH for t (11,14) (q13; q32) and immunohistochemistry for cyclin D1 on BM biopsy helped exclude mantle cell lymphoma [10]. Our case had a negative expression of surface IgM and dim expression of surface IgD. Although B-PLL usually shows bright surface IgM+/-IgD expression, few cases of B-PLL similar to our case with typical prolymphocyte morphology, bright B-cell antigen expression, and without surface IgM/IgG expression have been reported [11-13]. We report the current case
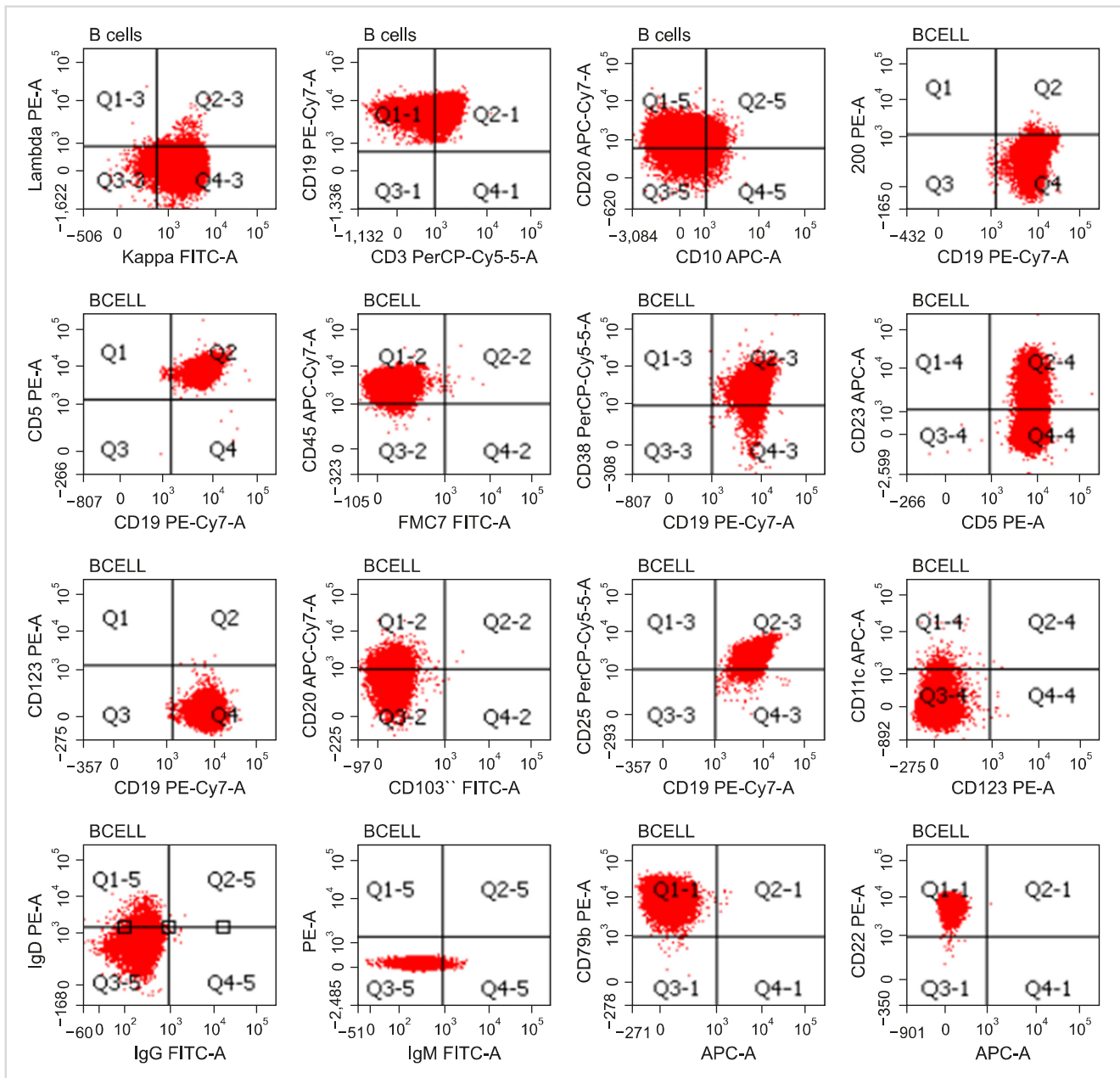
Fig. 2. Flow cytometry plots of the patient showing immunophenotype of the B-lymphocytes (red color). B-lymphocytes were CD45$^+$, CD5$^+$, CD23$^+$ (heterogeneous), CD200^{dim+}, CD19$^+$, CD20$^+$ (bright), surface CD22$^+$ (bright), surface CD79b$^+$ (bright), CD38$^+$, surface kappa$^+$ (bright), and surface IgD^{dim+}. CD10, FMC7, CD25, CD11c, CD123, CD103, surface lambda, IgG, and IgM were negative.

due to its rarity and potential diagnostic as well as therapeutic challenges. This report highlights that flow cytometry is suggestive; however, a combination of clinical, morphological, and immunophenotypical features is imperative to diagnose B-PLL.

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Rapid resolution of bone marrow necrosis mimicking relapse of pediatric acute lymphoblastic leukemia

TO THE EDITOR: Bone marrow (BM) necrosis is a rare clinicopathologic condition characterized by infarction of hematopoietic tissue [1]. Regarding pathophysiology, BM necrosis is characterized by disruption of BM microcirculation initiated by factors such as inflammatory vessel injury or mechanical vessel obstruction, and mediated through cytokines such as tumor necrosis factor [2]. Distinguishing features of BM necrosis include the acute onset of debilitating bone pain, fever, pancytopenia, and increased biochemical markers such as lactate dehydrogenase (LDH) and alkaline phosphatase (AP) [2]. The most common etiology of BM necrosis is the underlying malignant disease, particularly hematologic malignancies [3, 4]. Rarely, it may be caused by chemotherapy such as imatinib, all-trans-retinoic acid (ATRA), or arsenic trioxide, as well as immunotherapeutic agents [5-9]. In addition, granulocyte-colony stimulating factor (G-CSF), administered after chemotherapy to aid hematologic recovery, has been associated with the development of BM necrosis [10].

For patients with hematologic malignances, BM necrosis is most often diagnosed at time of initial disease presentation, or at relapse, underscoring the connection between leukemic blasts and necrotic pathology [2]. Identification of BM necrosis during chemotherapy while in complete remission (CR) of underlying disease is rare and can be alarming as the signs and symptoms of BM necrosis are similar to those observed at disease relapse.

Here, we report an adolescent T-cell acute lymphoblastic leukemia (ALL) patient who was diagnosed with sudden onset BM necrosis during sequential chemotherapy in first CR. We emphasize the clinical course of this patient as the characteristics of BM necrosis required differentiation from the possibility of ALL relapse. Furthermore, we were able to confirm rapid resolution of BM necrosis pathology.

A 16-year old male ALL patient was admitted for the 8th week of delayed intensification chemotherapy. Eight months previously, he had been diagnosed with T-cell ALL with *SIL-TAL1* rearrangement, and classified as very high risk due to age (15 years old) and initial white blood cell count (WBC) at diagnosis (375.71×10^9/L), according to our institution's risk group classification scheme [11]. He had achieved CR after remission induction chemotherapy, and had subsequently received consolidation and interim maintenance treatment phases without event. Intensification chemotherapy in the 8th week consisted of vincristine, dexamethasone, daunorubicin, cyclophosphamide, and asparaginase administered during a period of 1 week [11]. By the 3rd day of chemotherapy, complete blood count showed