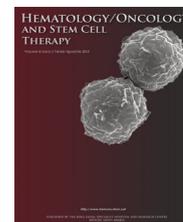




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## CASE REPORT

# Acute promyelocytic leukemia in a patient with chronic lymphocytic leukemia-A case report



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### KEYWORDS

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### Abstract

Chronic lymphocytic leukemia (CLL) is known to be associated rarely with myeloid malignancies such as acute myelogenous leukemia. In this article, we report an extremely rare occurrence of acute promyelocytic leukemia in a patient with CLL. A 71-year-old man first presented to our clinic with a diagnosis of CLL and worsening motor neuropathy symptoms. It was suspected that his CLL might be contributing to the neuropathy as a paraneoplastic syndrome, and he was treated with rituximab monotherapy in weekly doses for the 1st month and monthly treatments thereafter. By the end of his sixth monthly course of rituximab, the patient noted significant improvement in neuropathy symptoms but reported experiencing a new-onset worsening fatigue. He had new-onset cytopenias (white blood cells 1.6 k/ $\mu$ L, hemoglobin 11.7 g/dL, and platelet count 77 k/ $\mu$ L). A bone marrow examination was performed; it showed a high percentage of progranulocytes (21%), which stained positive for myeloperoxidase (MPO) and demonstrated a fine granular pattern on the promyelocytic leukemia (PML) oncogenic domain immunofluorescence test. The diagnosis of acute promyelocytic leukemia was confirmed by fluorescence in situ hybridization, which showed a PML/RAR $\alpha$  rearrangement in 46% of interphases. Flow cytometry was consistent with immunophenotype of acute promyelocytic leukemia and minimal residual CLL (0.07%). The patient was started promptly on all-trans-retinoic acid and arsenic trioxide induction regimen. Molecular remission was achieved after the first consolidation cycle. The patient is currently past his fourth consolidation cycle of

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all-trans-retinoic acid/arsenic trioxide and continues to be in complete remission. Our case illustrates that it is important for the physicians to be aware of coexistent hematologic and solid tumor malignancies in CLL, and maintain a low threshold for diagnostic testing based on grounds of low clinical suspicion.

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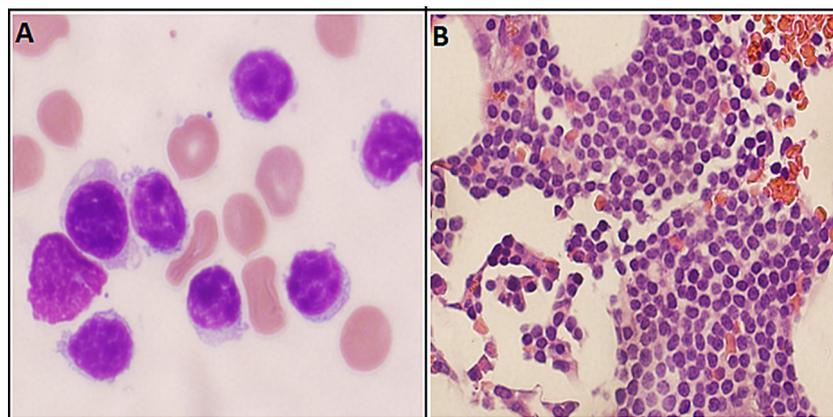
## Introduction

Chronic lymphocytic leukemia (CLL) is considered to be a state of immunosuppression and induces susceptibility to develop other cancers. Compared with the general population, patients with CLL are known to be at a higher risk for developing solid tumors such as lung cancer, melanoma, and hematologic malignancies such as Hodgkin's lymphoma [1–3]. CLL is also known to be associated with myeloid malignancies such as acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), almost all of which are therapy related (t-AML/MDS) [4–6]. Nevertheless, AML may also occur concurrent with or following untreated CLL [7,8]. The coexistence of acute promyelocytic leukemia (APL) and CLL is an extremely rare occurrence [9,10].

## Case report

A 71-year-old man first presented to our clinic after he was found to have an incidental bone marrow finding of CLL performed at an outside institution. He had a 3-year long history of small fiber sensory neuropathy for which he had undergone an extensive diagnostic workup. Most recent blood work from 6 months prior to the date of presentation showed immunoglobulin M paraproteinemia with an monoclonal spike (M-spike) of 0.1 mg/dL. He was diagnosed with possible Waldenstrom macroglobulinemia by his local oncologist, and treatment was offered. However, he presented to our hospital to obtain a second opinion. During this period, the patient's neurologist had treated him with

eight courses of plasma exchange, over a period of 2 months, which provided significant symptomatic relief from the neuropathy. On taking a detailed history, the patient endorsed noticing newly enlarged cervical lymph nodes, left ones being greater than the right ones, over the past 6 weeks. We repeated a bone marrow biopsy, which showed a CLL interstitial pattern involving 20% of the bone marrow and 5% nonclonal plasma cells (Fig. 1A and B). No aberrant blasts/myeloid populations were detected on bone marrow morphology at this time. He was found to have a deletion 13q by fluorescence in situ hybridization; immunoglobulin heavy chain (IGHV) mutation status was not tested. Meanwhile, the possibility of amyloidosis causing neuropathy was ruled out with a fat pad biopsy, and the mild M spike was attributed to monoclonal gammopathy of undetermined significance. A more comprehensive evaluation with a positron emission tomography scan disclosed multiple small lymph nodes with low standardized uptake value (SUV) uptake. As the patient was deemed to have a low-risk early-stage disease, he was placed under clinical observation. Over the next 8 months, the patient's neuropathy symptomatically got worse along with worsening gait imbalance. It was unclear if immunoglobulin M monoclonal gammopathy of undetermined significance was responsible for his neuropathic symptoms or if his CLL might have been contributing to the neuropathy as a paraneoplastic syndrome, and he was treated with rituximab monotherapy in weekly doses for the 1st month and monthly treatments thereafter. Of note, the patient's CLL was staged at Rai Stage I, with a white blood cell count of 15.6 k/ $\mu$ L (54% lymphocytes) at the time of initiation of rituximab. By the end



**Fig. 1** (A) Neoplastic lymphocytes from the 2014 bone marrow have features typical for CLL/SLL, with a homogeneous appearance, chromatin clumping, inconspicuous nucleoli, and scant cytoplasm (H&E, 400 $\times$ ). (B) The 2014 bone marrow biopsy specimen shows an interstitial expansion by the CLL/SLL cells (H&E, 400 $\times$ ). *Note.* CLL = chronic lymphocytic leukemia; H&E = hematoxylin and eosin; SLL = small lymphocytic lymphoma.

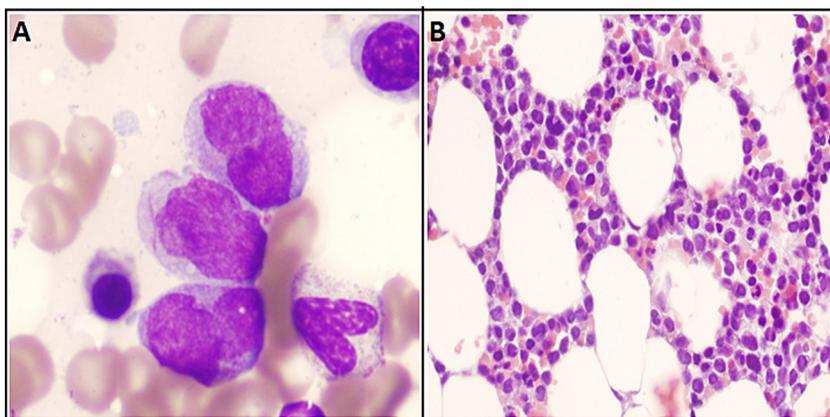
of his sixth monthly course of rituximab, the patient noted significant improvement in neuropathy symptoms, but reported experiencing a new-onset worsening fatigue. He had new-onset cytopenias (white blood cells 1.6 k/ $\mu$ L, hemoglobin 11.7 g/dL, platelet count 77 k/ $\mu$ L). Progressive CLL was suspected, and a bone marrow aspiration/biopsy was performed. Unexpectedly, the bone marrow showed a high percentage of progranulocytes (21%; Fig. 2A and B). The progranulocytes were abnormal with abundant Auer rods, stained positive for MPO, and demonstrated a fine granular pattern on the PML oncogenic domain immunofluorescence test [11]. Conventional cytogenetics revealed 46XY t(15; 17) (q24; q21) [5]/46XY [15], and the diagnosis of APL was confirmed by fluorescence in situ hybridization, which showed a PML/RAR $\alpha$  rearrangement in 46% of interphases. Four-color flow cytometry was consistent with the immunophenotype of APL (18% blasts; CD34 $^-$ , HLA-DR $^-$ , CD15 $^-$ , CD14 $^-$ , CD4 $^-$ , cCD3 $^-$ , CD19 $^-$ , CD11a $^-$ , CD18 $^-$ , CD117 $^+$ , CD64 $^+$ , CD123 $^+$ ) and minimal residual CLL (0.07%). The patient was diagnosed with APL with t(15; 17), and started promptly on all-trans-retinoic acid and arsenic trioxide induction regimen [12]. Day 21 bone marrow confirmed the patient to have achieved remission with 1% blasts and 2% progranulocytes (PML-RARA RT-PCR 9.9). Molecular remission was subsequently achieved after the first consolidation cycle. Minimal residual disease estimation by flow cytometry for CLL was not performed. The patient is currently past his fourth consolidation cycle of all  $^-$ trans-retinoic acid/arsenic trioxide and continues to be in complete remission. Subsequent bone marrow examinations since the time of APL diagnosis show no morphologic evidence of CLL or APL. On a repeat bone marrow evaluation, a year into remission, flow cytometry was positive for minimal residual CLL at 0.17%.

## Discussion

We report an extremely rare occurrence of APL in a patient with CLL. The patient had just completed treatment of CLL with rituximab monotherapy when he developed APL. At the time of development of APL, he had no morphologic

evidence of CLL in the bone marrow (minimal residual disease (MRD)-positive only). Occurrence of APL and CLL in the same patient has been rarely described (Table 1). Molero et al. [10] reported a 68-year-old patient with CLL who developed APL 2 years after receiving radiation therapy for prostate cancer. After treatment with idarubicin and all-trans-retinoic acid, the patient achieved complete remission for APL, albeit with continued persistence of the CLL population a year after therapy. APL was probably treatment related as unavoidable bone marrow exposures to high radiation doses posed an increased risk for leukemic transformation. Prognostic features and treatment of CLL were not reported [13,14]. Su et al. [9] reported APL and CLL in a 52-year-old patient who had not received any prior treatment including for CLL. The patient had been worked up with a diagnostic bone marrow for an incidental leukocytosis. Fluorescence in situ hybridization analysis demonstrated the presence of a t(15; 17) (q22; q12) translocation consistent with APL. A concurrently performed flow cytometry revealed a clonal B-cell population consistent with CLL. Although, the occurrence of secondary leukemias in association with CLL has previously been reported in literature, the coexistence of APL and CLL has not been documented individually [1–3,15].

It is pertinent to mention here that therapy-related APL is not an exceptional event and constitutes 12–15% of t-AML [13,16]. Therapy-related APL occurs typically after a latent period from the time of treating antecedent malignancies with alkylating agents and topoisomerase II inhibitors [13,16,17]. In addition, secondary leukemia is not known to be associated with the use of anti-CD20 antibodies such as rituximab. The possibility of CLL progression to high-grade clonally related lymphoma (Richter's transformation) is a well-described phenomenon [18]. However, several case reports and series suggest that CLL may transform into other forms of high-grade malignancies including acute leukemia. Zarrabi et al. [19] first reported a series of 31 leukemia patients with pre-existing CLLs, which were identified to be lymphoblastic leukemia in 10, myeloblastic leukemia in seven, and plasmacytic in one, and remained unidentified in 13 cases [19]. The first evidence of true clonal transformation from CLL to ALL was substantiated by Frenkel



**Fig. 2** (A) Neoplastic progranulocytes from the 2016 bone marrow specimen show variable nuclear irregularity with moderate amounts of hypergranular cytoplasm. The central progranulocyte contains multiple Auer rods (Wright stain, 1000 $\times$  oil). (B) The lack of granulocytic maturation past the progranulocyte stage is evident based on the uniformity of the neoplastic population in the interstitium. Note the marked nuclear irregularity and eosinophilic cytoplasm (H&E, 400 $\times$ ). Note. H&E = hematoxylin and eosin.

**Table 1** Case Reports Documenting CLL and a Concurrent Diagnosis of APL.

Reference	Patient age at APL diagnosis (y)	Therapy-related AML status	CLL status at emergence of APL	Treatment of APL	Outcome	CLL status at last follow-up
Molero et al. [10]	68	2 y post prostate cancer radiotherapy	40% marrow involvement	Idarubicin and all-trans-retinoic acid	Complete remission of APL 1 y later	Persistent disease, extent of disease not reported
Su et al. [9]	52	De novo	Peripheral blood lymphocytosis	All-trans-retinoic acid and hydroxyurea	Early death from hypoxic respiratory failure and disseminated intravascular coagulation	-
Current study	71	De novo	Minimal residual CLL (0.07%)	All-trans-retinoic acid and arsenic trioxide	Complete remission of APL 1 y later	Persistent minimal residual CLL (0.17%)

Note. AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; CLL = chronic lymphocytic leukemia; y = year.

et al. [20] using flow cytometry analysis [20]. These transformations are not necessarily a product of prior chemotherapy [21,22]. Most examples described in the literature are lymphoid lineage transformations. Transformation of chronic lymphoid neoplasms to myeloid malignancies is scarce and has only recently been reported [23,24]. The phenomenon of hematopoietic lineage plasticity with trans-differentiation of lineage-specific cells is only beginning to be understood [25,26]. We did not undertake clonality analysis testing to look for a relation between the two cell populations.

It is more likely that the APL and CLL in our patient represented two simultaneously occurring but separate disease processes arising from different progenitor pathways [7]. It is plausible that rituximab may have allowed the clinical emergence of APL clone (by suppressing the CLL clone). Ansari et al. [27] reported on a case of patient who developed acute myeloid leukemia AML a cycle after chemotherapy in CLL [27]. Intriguingly, the bone marrow examination at the time of the CLL diagnosis revealed a small population of abnormal immature myeloid cells. It is posited that CLL clone may be producing cytokines suppressive to the growth of AML cells, thereby allowing their clinical emergence on eliminating the CLL clone [4,27,28]. Alternatively, rituximab treatment may have further impaired the already hampered immunosurveillance associated with CLL. Rituximab interferes with antigen-presenting function of normal B cells, depletes normal B-cell clones, and impairs humoral responses against the tumor antigens [29]. In fact, AML relapses are known to occur after rituximab treatment for post-transplant GVHD attesting to the role in normal B lymphocytes in mediating antitumor responses [30].

In conclusion, we report an extremely rare case of APL concurrent with CLL. It is important for the physicians to be aware of coexistent hematologic and solid tumor malignancies in CLL, and maintain a low threshold for diagnostic testing based on grounds of low clinical suspicion.

## Acknowledgments

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## Conflict of interest

There are no conflicts of interest to disclose.

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