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ORIGINAL ARTICLE

Non-Hodgkin lymphoma mimicking acute leukemia: a report of six cases and review of the literature

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Abstract

Aggressive subtypes of non-Hodgkin lymphoma may uncommonly be referred to clinical oncologists for treatment of acute leukemia, due to an elevated or rapidly rising white blood cell count (WBC), with circulating neoplastic cells that morphologically resemble leukemic blasts seen in acute myeloid or lymphoblastic leukemia. We describe six cases of non-Hodgkin lymphoma that mimicked acute leukemia and were identified in the pathology records of the Brigham and Women's Hospital. The patients were older adults (mean age 70 years), who presented with leukocytosis (mean 79.7×10^9/L) with circulating neoplastic cells (mean 57%), which mimicked leukemic blasts, thrombocytopenia, and anemia (4/6 patients). In each case, immunophenotypic analysis identified a population of mature B cells or mature T cells. We identified 15 additional cases of non-Hodgkin lymphoma in the literature that mimicked acute leukemia; considering all 21 cases, 11 had an appearance of acute lymphoblastic leukemia, 4 had an appearance of acute monocytic leukemia, and 6 had an appearance of acute leukemia unable to be further categorized. In general, patients exhibited poor overall survival. These cases illustrate the importance of comprehensive immunophenotypic analysis in the initial evaluation of hematolymphoid neoplasms, and that occasional cases of non-Hodgkin lymphomas can resemble acute leukemia at initial presentation.

Keywords Peripheral T cell lymphoma, NOS · Burkitt lymphoma · Diffuse large B cell lymphoma, high-grade B cell lymphoma, B cell prolymphocytic leukemia · Flow cytometry · Immunohistochemistry

Introduction

Aggressive subtypes of non-Hodgkin lymphoma often present with advanced stage disease and may involve lymphoid tissue, extranodal sites, and bone marrow and peripheral blood [1]. Uncommonly, such patients may be referred to clinical oncologists for treatment of acute leukemia due to an elevated or rapidly rising white blood cell count (WBC), with circulating neoplastic cells that morphologically resemble leukemic blasts seen in acute myeloid leukemia or acute lymphoblastic leukemia. In such cases, comprehensive immunophenotypic analysis using a flow cytometric and/or immunohistochemical approach, along with correlation with other clinical, laboratory, cytogenetic, and radiologic findings, can serve to identify non-Hodgkin lymphoma as the correct diagnosis. Here we report six cases of non-Hodgkin lymphoma that were referred to clinical oncologists for acute leukemia treatment, based on a preliminary outside hospital, Emergency Department (ED), or medical clinic assessment of clinical and/or peripheral blood findings. In addition, we have identified 15 additional cases of non-Hodgkin lymphoma in the literature that mimicked acute leukemia and summarize the overall findings.

Materials and methods

Cases of non-Hodgkin lymphoma that presented with peripheral blood findings suggestive of acute leukemia based on preliminary outside hospital or clinic assessment of peripheral blood findings were identified in the pathology records of the Brigham and Women's Hospital. Peripheral blood and bone marrow aspirate smears, histologic sections, immunohistochemical, and flow cytometric studies

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performed at the time of diagnosis were reviewed, along with clinical, other laboratory, and radiologic findings. The findings in one of the cases were previously reported [2].

Results

Six recent cases of non-Hodgkin lymphoma presented at outside hospitals, the ED, or a local medical clinic with clinical and peripheral blood findings suggestive of acute leukemia and were referred to medical oncologists at our institution for treatment; the results are summarized in Table 1.

Case 1

The findings in this case were previously reported [2], and are briefly summarized here. A 70-year-old man presented with a 2-week history that included anemia (hemoglobin = 12.2 g/dL, Hct = 34.5%), thrombocytopenia (13.0×10^9/L), and a rapidly rising white blood cell count (43.3 to 74.9×10^9/L over 4 days), with 72% abnormal, intermediate- to large-sized cells on the peripheral blood smear that had an immature, pleomorphic appearance, and were thought to be monocytic blasts on preliminary examination at an outside hospital (Fig. 1A–B). Flow cytometric findings were consistent with a mature T cell neoplasm, with positivity for pan-T cell markers CD3, CD5, CD4 (weak), CD8 (weak), and absence of staining for T cell and NK cell markers CD2, CD7, CD16, CD25, CD56, CD57, myeloid, monocytic, and B cell markers, as well as CD1a, TdT, and CD34. A bone marrow biopsy and biopsy of one of two new scalp lesions both contained an extensive infiltrate of cells with an appearance similar to that seen in the peripheral blood (Fig. 1C). Immunohistochemical staining correlated with the flow cytometric findings, and revealed, in addition, that the neoplastic cells were positive for T cell receptor (TCR) Beta F1, and negative for TCR delta chain, CD30, TCL1, Perforin, Granzyme, FOXP3, CD103, ALK1, and PD-1, with a Ki-67 proliferation index of ~ 80–90%. In situ hybridization for Epstein-Barr virus encoded small RNAs (EBER) was negative. Cytogenetic findings were complex, and not diagnostic of any particular neoplasm. Molecular analysis revealed pathogenic single nucleotide variants in *STAT5B* (c.1924A > C (p.N642H); 92.1% VAF) and *NRAS* (c.181C > A (p.Q61K); 5.9% VAF). Subsequently, the patient was also found to have multistation lymphadenopathy by computed tomography of the chest. The overall findings were most in keeping with involvement by peripheral T cell lymphoma, NOS, and were not characteristic of other mature T cell neoplasms, including adult T cell leukemia/lymphoma, T cell prolymphocytic leukemia, and Sezary syndrome. The patient began initial treatment with cyclophosphamide and methylprednisolone, developed tumor lysis syndrome, then shock, and expired 1 week later.

Case 2

A 68-year-old woman presented to an outside hospital with fatigue, epistaxis, anorexia, oral lesions, anemia (hemoglobin = 7.0 g/dL, Hct = 21.0%), thrombocytopenia (76.0×10^9/L), and an elevated white blood cell count (14.0×10^9/L), with 29% circulating immature cells concerning for leukemic blasts and involvement by lymphoblastic leukemia (Fig. 2A–B). Bone marrow aspirate smears were aspicular but cellular with cellularity virtually entirely composed of small- to intermediate-sized cells with round to slightly irregular nuclei, moderately dispersed chromatin, multiple small nucleoli, and scant amounts of deeply basophilic cytoplasm with striking vacuolization (Fig. 2C). The bone marrow core biopsy was variably cellular, overall moderately hypercellular (30% fat), with approximately 90% of the cellularity (60% of

Table 1 Summary of cases of non-Hodgkin lymphoma presenting as acute leukemia

Case	Age, sex	WBC at presentation	% abnormal cells in peripheral blood	Anemia	Thrombocytopenia	CNS involvement	Clinical impression	Final diagnosis
1	70, M	$43.3–74.9 \times 10^9$/L	72%	Yes	Yes	No	Acute monocytic leukemia	Peripheral T cell lymphoma, NOS
2	68, F	14.0×10^9/L	29%	Yes	Yes	Yes	Acute lymphoblastic leukemia	Burkitt lymphoma
3	62, M	18.9×10^9/L	30%	No	Yes	Yes	Acute leukemia	High-grade B cell lymphoma, NOS
4	71, F	188.5×10^9/L	86%	Yes	Yes	Yes	Acute leukemia	DLBCL
5	73, M	54.2×10^9/L	65%	Yes	Yes	No	Acute leukemia	B-prolymphocytic leukemia
6	78, F	99.6×10^9/L	61%	No	Yes	No	Acute monocytic leukemia	Aggressive B cell lymphoma

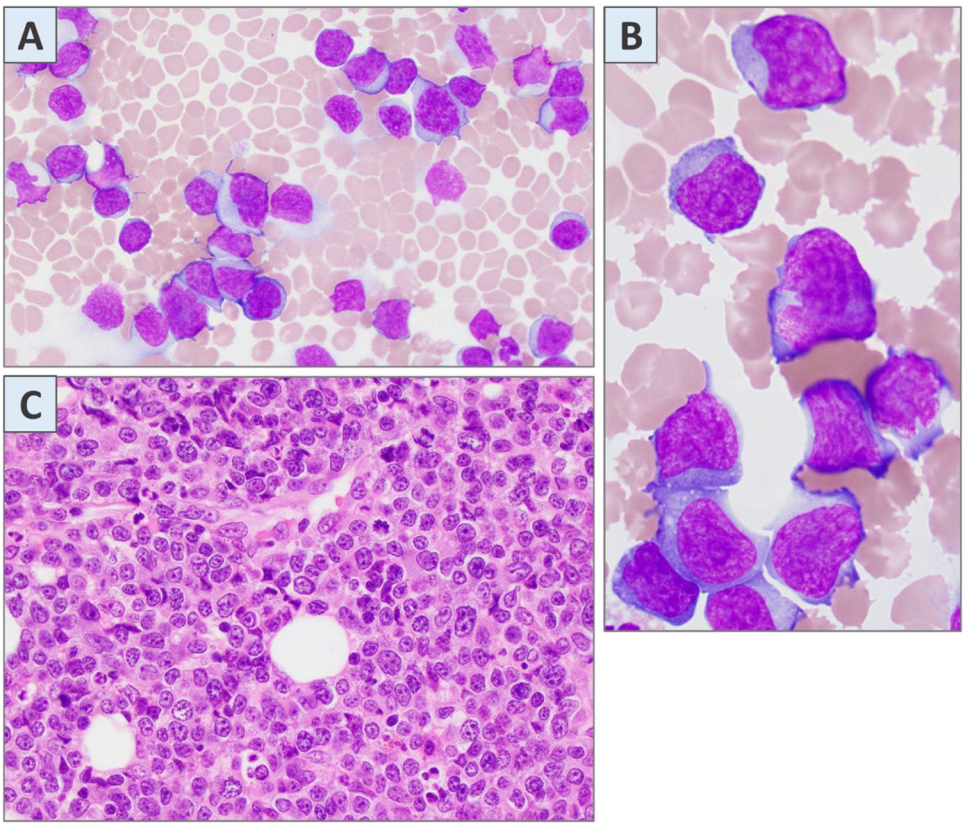

Fig. 1 **A–B** Intermediate- to large-sized neoplastic cells present in the peripheral blood smear that were thought to be monocytic blasts on preliminary examination at an outside hospital (Wright-Giemsa stain, original magnification × 500 and × 1000). **C** Hypercellular bone marrow biopsy containing approximately 95% intermediate- to large-sized neoplastic cells with irregular nuclei, mostly dispersed chromatin, small nucleoli, and small amounts of cytoplasm (hematoxylin and eosin, original magnification × 400)

the intertrabecular space) composed of an infiltrate of cells similar to those seen in the bone marrow aspirate. Karyorrhectic debris and frequent mitotic figures were present (Fig. 2D). Immunoperoxidase studies showed that the neoplastic cells were CD20 positive B cells which were also positive for CD10, BCL6, MYC, and negative for BCL-2, MUM1, CD34, and TdT. The Ki67 proliferation index was very high (> 95%). In situ hybridization for EBER was positive. Flow cytometric analysis performed on the bone marrow aspirate showed a population of B cells (44% of gated events; 24% of total events) with moderate CD45 expression that were positive for B lymphoid markers CD19, CD20, and co-expressed CD10, and CD38, exhibited dim monotypic staining for surface immunoglobulin kappa, and were negative for CD5, CD23, CD11c, CD34, TDT, and other myeloid, monocytic, and T cell markers, in a background of polytypic, CD10-negative B cells consistent with involvement by a CD10 positive mature B cell lymphoma.

Cytogenetic analysis showed a 46,XX,t(8;14)(q24;q32)[20] karyotype. Molecular analysis revealed pathogenic single nucleotide variant and small deletion, in *TP53* (c.733G > A (p.G245S); 43.1% VAF) and *PPM1D* (c.1283_1286delCAAG (p.P428Rfs*2) 0.5% VAF). The overall findings were consistent with bone marrow involvement by Burkitt lymphoma. The patient was subsequently found to have supraclavicular lymphadenopathy and central nervous system (CNS) involvement, and began treatment with R-EPOCH multiagent chemotherapy.

Case 3

A 62-year-old man presented to an outside hospital with a 1 week prodrome of fatigue, night sweats, and then 3-day history of vomiting, and was found to have leukocytosis (white blood cell count = 18.9×10^9/L), with 30% of cells classified as blasts with immature appearing chromatin and deeply basophilic cytoplasm with prominent vacuoles (Fig. 3A–B). Hemoglobin was 14.8 g/dL but he had thrombocytopenia (44×10^9/L). He had concomitant renal failure and tumor lysis syndrome (uric acid = 28.9 mg/dL, creatinine = 4.77 mg/dL, LDH = 2150 U/L). The presumed clinical diagnosis was acute leukemia and the patient was transferred to our hospital, at which time peripheral blood flow cytometry was performed and showed aberrant B cells with dim CD45 expression, positivity for HLA-DR, CD19 (bright), CD20 (bright), and CD38 (bright), which exhibited dim surface immunoglobulin kappa light chain expression, and were negative for CD5, CD10, CD11c, CD23, CD15, CD56, CD123, TdT, lambda light chain, and other myeloid, monocytic, and T cell markers. Although the overall immunophenotypic findings favored a mature B cell neoplasm,

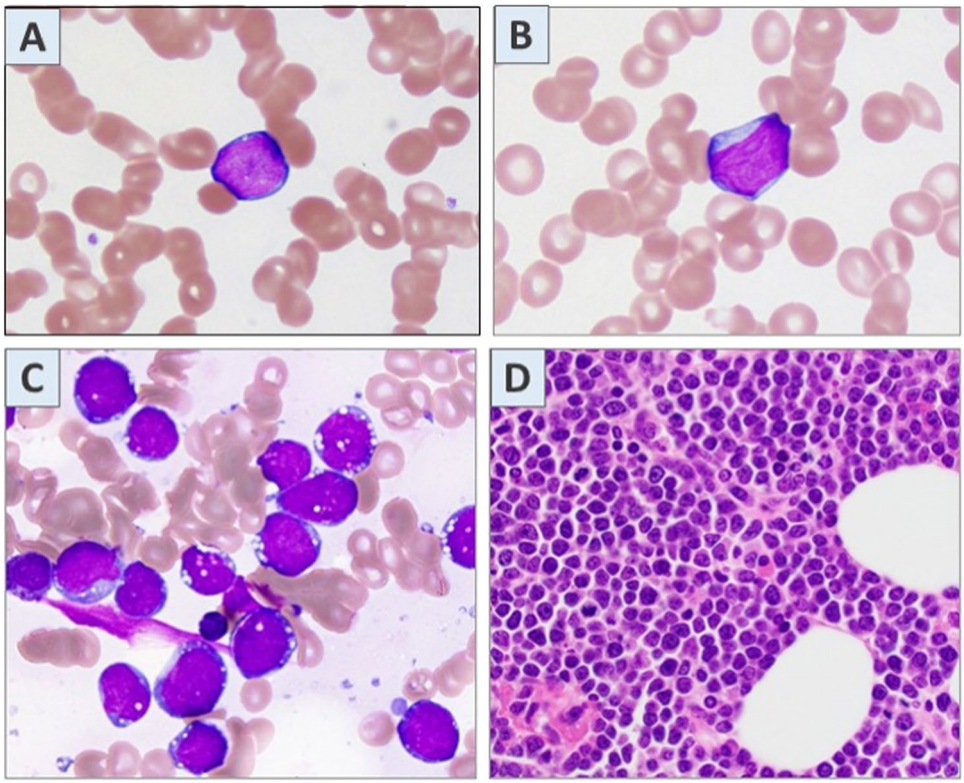

Fig. 2 **A**–**B** Small- to intermediate-sized neoplastic cells present in the peripheral blood smear that were thought to be lymphoblasts on preliminary examination at an outside hospital (Wright-Giemsa stain, original magnification × 1000). **C** The bone marrow aspirate was aspicular but cellular, with 95% of the cellularity consisting of small- to intermediate-sized cells with round to slightly irregular nuclei, moderately dispersed chromatin, multiple small nucleoli, and scant amounts of deeply basophilic cytoplasm with striking vacuolization (Wright-Giemsa stain, original magnification × 1000). **D** The bone marrow biopsy was moderately hypercellular (30% fat), with approximately 90% of the cellularity (60% of the intertrabecular space) composed of an infiltrate of medium-sized lymphoid cells with slightly irregular nuclei, opened chromatin, prominent nucleoli, and moderate amounts of cytoplasm. Karyorrhectic debris and frequent mitotic figures were present (hematoxylin and eosin, original magnification × 400)

given the dim CD45 expression and immature-appearing chromatin, definitive classification was deferred to additional studies. PET-CT imaging showed FDG avid disease throughout the marrow, spleen, and small FDG avid bilateral cervical and left supraclavicular nodes, and retroperitoneal and mesenteric involvement.

The bone marrow aspirate was aspicular, and consisted mostly of medium- to large-sized cells similar to those seen in the peripheral blood (Fig. 3C). A bone marrow biopsy showed extensive (> 95%) involvement by sheets of medium- to large-sized mononuclear cells with round to slightly irregular nuclei, somewhat dispersed chromatin, distinct nucleoli (often multiple, occasionally prominent), and small amounts of cytoplasm, with numerous mitotic figures and occasional debris (Fig. 3D). By immunostaining, the cells were CD20, CD79a positive B cells which co-expressed CD10 (dim), and C-MYC (strong, > 90%), and were negative for BCL2 (three clones tested — 124, E17, SP66), MUM1, TdT, cyclin D1, and CD34. Ki67 proliferation index was high (> 80–90%). In situ hybridization studies for EBV-encoded RNA (EBER) were negative. Cytogenetics showed 46,XY[cp20] and interphase FISH analysis did not demonstrate *MYC*, *IGH-BCL2*, or *BCL6* rearrangements. Molecular analysis revealed pathogenic single nucleotide variants and small deletions in *MYC* (c.218C > T (p.T73I), 42.1% VAF), *TET2* (c.4354C > T (p.R1452*), 43.3% VAF), *TP53* (c.818G > A (p.R273H), 34.7% VAF), and *CXCR4* (c.839_840delTG (p.V280Afs*30), 26.5% VAF). The final integrated diagnosis was high-grade B cell lymphoma (HGBL), not otherwise specified (NOS), with Burkitt-like features. He was treated with R-EPOCH, initially complicated by a seizure and non-traumatic epidural bleed, but completed 3 cycles with initial response. Subsequently, he developed extensive leptomeningeal disease and treated with HD-MTX and R-CHOP, but developed cauda equina syndrome requiring radiation, but the CNS involvement rapidly progressed and his care was transitioned to comfort measures only.

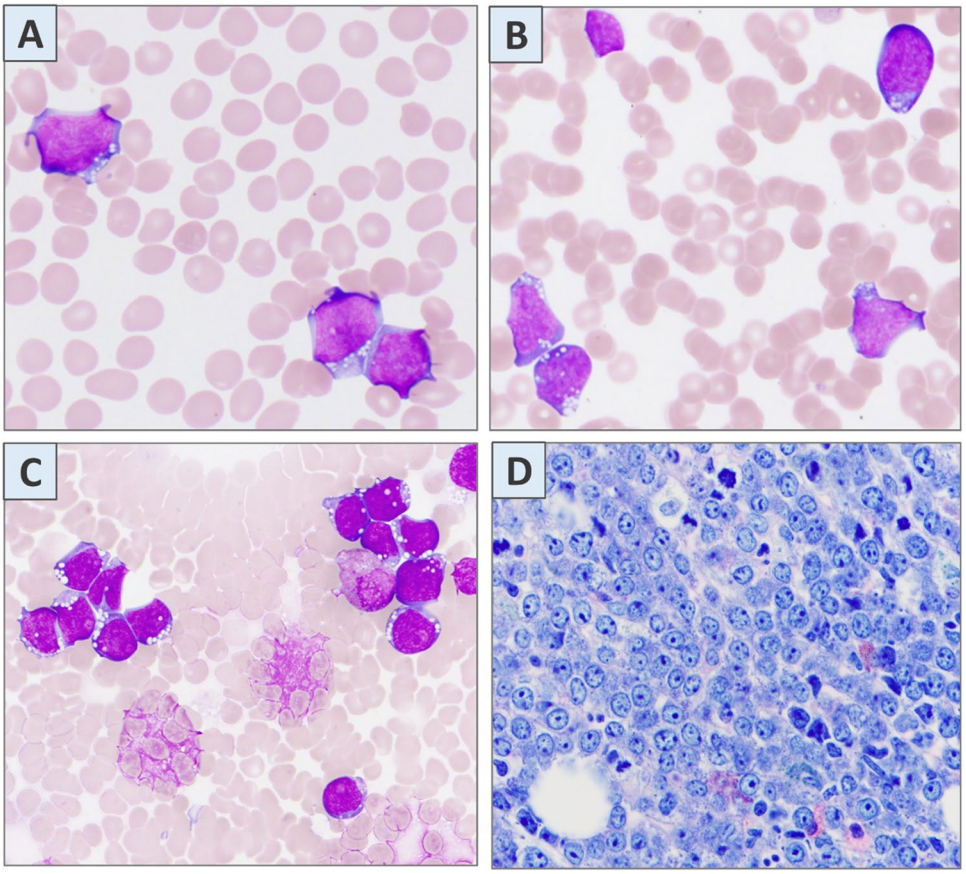

Fig. 3 **A–B** Intermediate- to large-sized neoplastic cells present in the peripheral blood smear, with round to irregular nuclei, immature appearing chromatin, and basophilic cytoplasm with occasional vacuoles, classified as blasts at an outside hospital (Wright-Giemsa stain, original magnification × 1000). **C** The bone marrow aspirate was aspicular, but the limited cellularity consisted mostly of medium- to large-sized cells with irregular nuclei, moderately dispersed chromatin, variably distinct nucleoli, and scant to moderate amounts of deeply basophilic cytoplasm with prominent vacuoles (Wright-Giemsa stain, original magnification × 1000). **D** Hypercellular bone marrow biopsy containing > 95% intermediate- to large-sized neoplastic cells with slightly irregular nuclei, somewhat dispersed chromatin, prominent nucleoli (often multiple), and variable amounts of cytoplasm, with frequent mitotic figures (Giemsa stain, original magnification × 500)

Case 4

A 71-year-old woman presented to the ED with fatigue and increasing shortness of breath. Two months prior, she had reported to an outside clinic with intermittent mild cervical lymphadenopathy in the setting of a mild COVID-19 infection, at which time she had a normal WBC, and an FNA biopsy of a lymph node was favored to be reactive. In the ED, she was found to have profound anemia (hemoglobin = 4.9 g/dL, Hct = 15.5%), thrombocytopenia (101.0×10^9/L), and markedly elevated white blood cell count (188.5×10^9/L), with 86% of cells flagged as immature in appearance, with irregular or lobated nuclei and prominent nucleoli, concerning for acute leukemia (Fig. 4A–B). Flow cytometric analysis of peripheral blood revealed a population of abnormal B cells positive for CD19, and CD20(dim), co-expressing CD10, CD5, CD25, and CD38, with monotypic surface immunoglobulin kappa, and negative for CD23, CD11c, CD103, TDT, CD34, CD117, CD13, CD33, CD56, CD64, and other T cell markers, most consistent with a mature B cell lymphoma, with unusual co-expression of CD5 and CD10. A bone marrow biopsy was performed showing greater than 95% involvement by sheets of cells similar in appearance to those seen in the peripheral blood, with regions of necrosis. Immunostaining confirmed that the cells were PAX5 + B cells that co-expressed BCL-2 and were negative for LEF-1, CD43, cyclin D1, SOX11, BCL-6, MUM-1, CD30, CD200, c-MYC (30%, weak), ALK1, TdT, and EBER (in situ hybridization for EBV RNA). Cytogenetic studies showed the following complex clonal aberrations, which were not specific to any particular type of neoplasm:

43,X,-X,del(1)(p13),?t(6;9)(p11.1;q34),?t(6;11)(p11.1;q23),add(9)(q13),-12,-13,-14,?t(15;17)(p11.2;q25),t(20;22)(p13;p11.2),+21[4],+mar1[11],+mar2[2][cp19]/46,XX[1].nuc ish(MYCx3)[60/100]. Molecular analysis revealed pathogenic single nucleotide variants in *TP53* (c.832C > G (p.P278A), 92.9% VAF) and *ATM* (c.5623C > T (p.R1875*), 78.2% VAF).

The overall findings were of a CD5, CD10 positive large B cell lymphoma presenting with a significant circulating component. Definitive classification was difficult but most consistent with diffuse large B cell lymphoma, with prolymphocytic leukemia-like features. PET-CT imaging showed significant FDG uptake throughout the entire skeleton and spleen, and mild FDG uptake in mildly enlarged supra- and sub-diaphragmatic nodes (largest 3.2 cm). She was treated with 6 cycles of R-CHOP with initial response, but subsequently progressed with development of significant leptomeningeal involvement. She received radiation to L1 sacrum

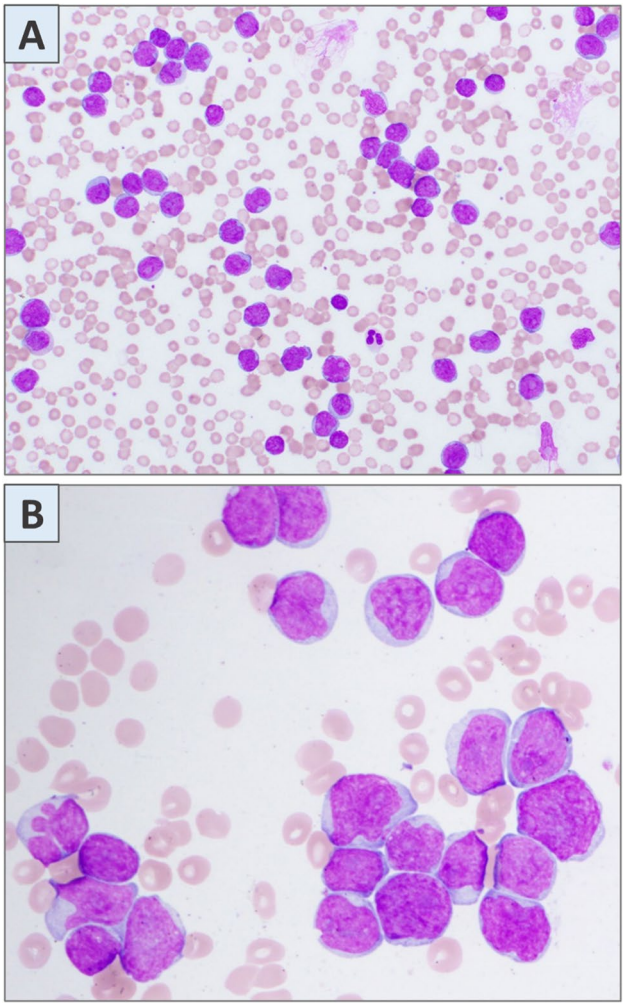

Fig. 4 **A**–**B** Marked leukocytosis with intermediate- to large-sized neoplastic cells in the peripheral blood smear, with irregular or lobated nuclei, somewhat dispersed chromatin, variably prominent nucleoli, and moderate amounts of pale cytoplasm, initially designated as blasts and presumed to be an acute leukemia (Wright-Giemsa stain, original magnification × 500 and × 1000)

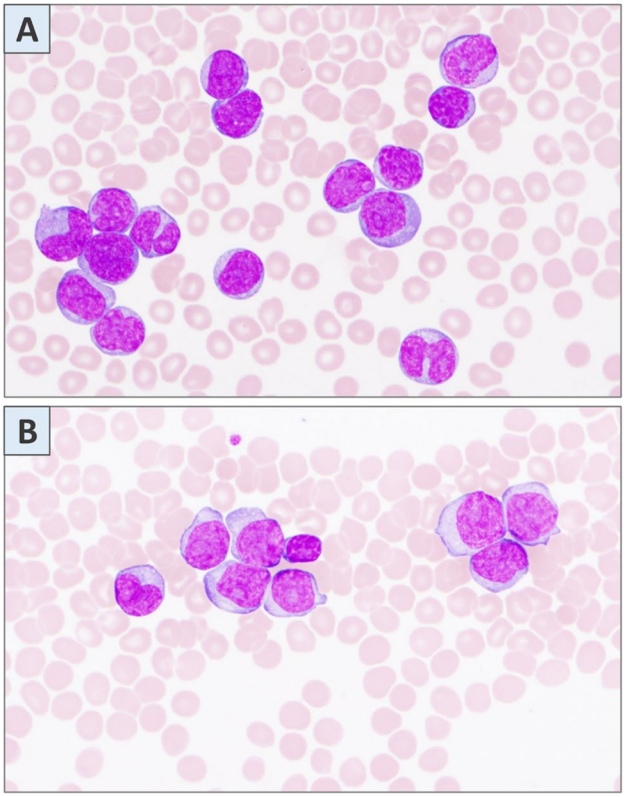

Fig. 5 **A**–**B** Leukocytosis with large-sized neoplastic cells that have round to irregular nuclei, variably coarse chromatin, prominent nucleoli, and moderate amounts of pale cytoplasm, favored to represent blasts on initial assessment at an outside hospital, leading to patient's admission to our leukemia service (Wright-Giemsa stain, original magnification × 1000)

for cauda equina syndrome, then three cycles of high dose methotrexate, but further progressed with worsening CNS and systemic disease, ultimately transitioned to hospice comfort care.

Case 5

A 73-year-old man presented to an outside hospital with fever, fatigue, and cough, presumed to be pneumonia. He was found to have a markedly elevated white blood cell count (54.2×10^9/L), with 68% cells that were large-sized, with round to irregular or occasionally lobated nuclei, variably coarse chromatin, prominent nucleoli, and moderate amounts of pale cytoplasm, favored to represent blasts, and a diagnosis of acute leukemia (Fig. 5A–B). He had anemia (hemoglobin = 9.0 g/dL, Hct = 27.4%) and thrombocytopenia (53.0×10^9/L). He was admitted to our hospital's acute leukemia service, and as part of a comprehensive workup, flow cytometry was submitted which showed B cells positive for CD19, and CD20 (moderate to bright), co-expressing CD5 and CD23 (variable), with monotypic staining for surface immunoglobulin kappa (moderate intensity), but negative for CD10, CD11c, CD38, CD34, and other T cell markers and myeloid markers. PET-CT imaging showed low avidity, small volume adenopathy above and below the diaphragm with significant splenomegaly. A bone marrow biopsy showed extensive (> 90%) involvement by sheets of cells similar in appearance to those seen in the peripheral blood. Immunostains showed that the neoplastic B cells were positive for CD20, and negative for cyclin D1, Sox11, and TdT. LEF1 appeared weakly positive. Cytogenetics showed complex clonal aberrations including deletions of 5q, 7q, and 17p. 44,Y,add(X)(q22),-1,add(2)(q35),add(3)(p25), add(4)(p14),del(5)(q31q35),add(6)(p23),der(6)t(6;7)(p21;q11.2),-7,i(8)(q10), del(14)(q32),-15, add(16)(p13.3),add(16)(q24),-17,del(17)(p13) + 2mar[20]. Molecular analysis

revealed a pathogenic small deletion in *TP53* (c.797delG (p.G266Dfs*79); 85.1% VAF).

The overall clinical, morphologic, immunophenotypic, and molecular genetic findings were most in keeping with B cell prolymphocytic leukemia, with a complex karyotype and *TP53* mutation. He was started on acalabrutinib, with little response, then treated with obinatuzumab, with initial dramatic improvement in circulating disease, but complicated by renal failure, developed fungemia and rapid respiratory failure, and ultimately transitioned to comfort measures and died.

Case 6

This patient was a 78-year-old woman, who initially in 2014 had been diagnosed with a B cell lymphoma ultimately favored to be splenic marginal zone lymphoma. She had received bendamustine plus rituximab, and subsequently underwent splenectomy in 2016. She was observed until presenting with weight loss in 2019, at which time was found to have a dominant liver mass, and extensive bony uptake on PET-CT imaging. A liver biopsy was consistent with diffuse large B cell lymphoma, NOS, with no rearrangements in *MYC*. The patient received 6 cycles of R-CHOP, and post treatment imaging was consistent with a complete response. At the time her CBC was reportedly normal. One year later, at a routine follow-up visit, she was found to have a markedly elevated white blood cell count (99.6×10^9/L), with 61% cells flagged as immature monocytes. Hemoglobin was 14.0 g/dL but she had mild thrombocytopenia (121×10^9/L). Over the course of 3 weeks, her WBC rapidly increased to 187.1×10^9/L, with 70% of cells showing medium- to large-sized nuclei, round to irregular nuclei, slightly dispersed chromatin, frequent prominent nucleoli, with moderately abundant pale blue cytoplasm and occasional vacuoles, resembling monoblasts (Fig. 6A–B), concerning for acute monocytic leukemia. Flow cytometric immunophenotyping showed B cells that were positive for CD19, CD20 (variable), that co-expressed CD11c (subset), exhibited monotypic staining for surface immunoglobulin kappa, and were negative for CD10, CD5, CD23, CD38, and other T cell markers. The bone marrow biopsy showed greater than 90% involvement by cells similar in appearance to those seen in the peripheral blood. Molecular analysis revealed pathogenic single nucleotide variants and a small deletion, in *NOTCH2* (c.6855_6876delGAGCAGGCCACCTGAAGGGAAG (p.Q2285Hfs*3); 8.1% VAF), *NOTCH2* (c.6442_6443delTT (p.L2148Ifs*4); 1.6% VAF), and *PPM1D* (c.1654C > T (p.R552*); 5.4% VAF). The overall findings were consistent with a mature B cell lymphoma with aggressive clinical features, difficult to further classify. Shortly thereafter, she suffered an intraparenchymal brain hemorrhage in the setting of a mechanical fall. After extensive discussions with patient and family, her care was focused on palliation of symptoms.

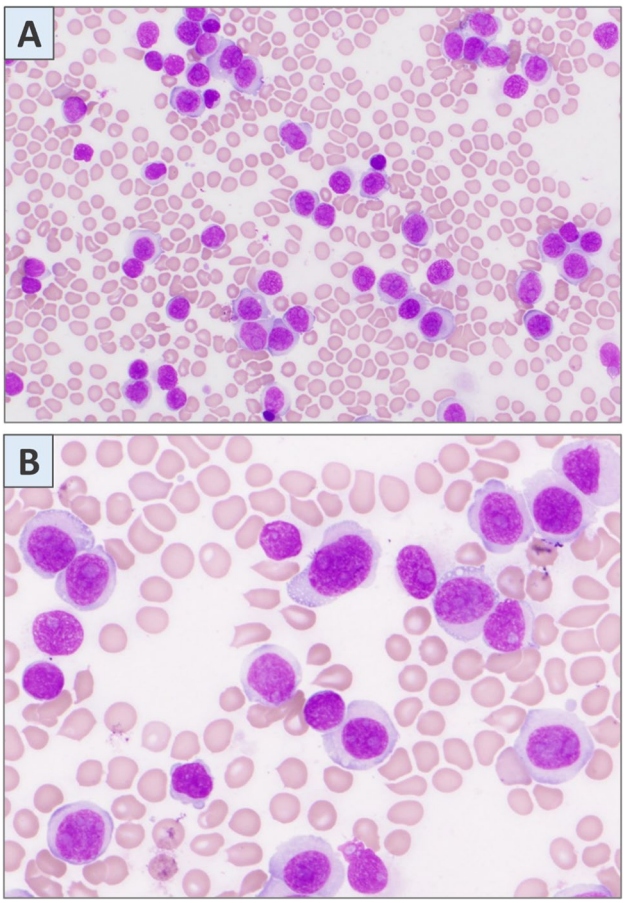

Fig. 6 **A–B** Marked leukocytosis with large-sized neoplastic cells with round to ovoid nuclei, moderately dispersed chromatin, occasional nucleoli, and moderate to highly abundant pale blue cytoplasm with occasional fine vacuoles; thought to resemble immature monocytes and monoblasts, with concern for a monocytic leukemia (Wright-Giemsa stain, original magnification × 500 and × 1000)

Summary of findings

In summary, the patients were older adults (mean age 70.3 years) with an equal sex distribution (3 men, 3 women), all of whom presented with leukocytosis (mean 79.7×10^9/L) with circulating neoplastic cells (mean 57%), which mimicked leukemic blasts (Table 1). All six patients were thrombocytopenic, and 4 of 6 were anemic at presentation. Three of 6 six patients had neoplastic cells present in cerebrospinal fluid and all 6 patients had extensive bone marrow involvement (≥ 90% of cellularity). In each case, the neoplastic cells were found to be mature B cells (5 of 6 cases) or mature T cells (1 of 6 cases) by flow cytometric immunophenotyping and immunohistochemical staining; 5 cases analyzed

for expression of myeloid markers, TdT, and CD34 were negative. Cytogenetic findings were helpful for diagnosis in one case of Burkitt lymphoma, and were complex in three other cases. Molecular analysis revealed multiple somatic mutations, including mutations in *TP53* in 4 of 6 cases. Five of six patients were initially treated with multiagent chemotherapy, but the patients exhibited poor overall survival; one patient responded to treatment, 2 patients died, and 3 patients were transitioned to end-of-life care.

Additional cases in the medical literature

We identified 15 additional cases of non-Hodgkin lymphoma previously reported in the medical literature that mimicked acute leukemia [3–9]; the results are summarized in Table 2. Patients ranged in age from 13 to 94 years, included 11 men and 4 women, all of whom presented with leukocytosis and/or lymphocytosis and circulating neoplastic cells with a blast-like appearance. Based on immunophenotypic analysis, neoplastic cells were found to be mature B cells in 11 of 15 cases and mature T cells in 4 of 15 cases, which included three cases of hepatosplenic T cell lymphoma and one case of peripheral T cell lymphoma, NOS, initially mistaken for T cell acute lymphoblastic leukemia, two cases of DLBCL, initially mistaken for acute monocytic leukemia, three cases of HGBL with *MYC* and *BCL2* or *BCL6* rearrangement (double hit lymphoma), initially mistaken for acute leukemia, and six cases of blastoid mantle cell lymphoma initially mistaken for acute lymphoblastic leukemia. In general, patients exhibited poor overall survival: of the 10 patients with follow-up information, 7 patients died between 2 weeks and 18 months following initial treatment.

Considering all 21 cases described, 11 cases had an appearance of acute lymphoblastic leukemia, including one case of Burkitt lymphoma, 3 cases of hepatosplenic T cell lymphoma, six cases of blastoid mantle cell lymphoma, and one case of peripheral T cell lymphoma, NOS. Four cases had an appearance of acute monocytic leukemia, including one case of peripheral T cell lymphoma, NOS, one case of aggressive B cell lymphoma unable to be further categorized, and 2 cases of diffuse large B cell lymphoma. Six cases had an appearance of acute leukemia unable to be further categorized, including 4 cases of HGBL, one of which was HGBL, NOS, and three of which were double hit

Table 2 Additional cases of non-Hodgkin lymphoma presenting as acute leukemia from the medical literature

Case	Age, sex	WBC at presentation	% abnormal cells in peripheral blood	Anemia	Thrombocytopenia	Clinical impression	Final diagnosis	Ref
1–3	13–17 2F, 1 M	Lymphocytosis	17–91%	N/A	N/A	Acute lymphoblastic leukemia (all three cases)	Hepatosplenic T cell lymphoma	[3]
4	62, F	14.9×10^9/L	Occasional*	Yes	No	Acute monocytic leukemia	Diffuse large B cell lymphoma	[4]
5	60, M	191.3×10^9/L	91%	N/A	N/A	Acute leukemia	High-grade B cell lymphoma (double hit lymphoma)	[5]
6	64, M	21.7×10^9/L	38%	Yes	Yes	Acute leukemia	High-grade B cell lymphoma (double hit lymphoma)	[6]
7	55, M	$>400\times10^9$/L	Numerous	Yes	Yes	Acute leukemia	High-grade B cell lymphoma (double hit lymphoma)	[6]
8	71, M	$14.5–10^6\times10^9$/L	43%	No	No	Acute lymphoblastic leukemia	Peripheral T cell lymphoma, not otherwise specified	[7]
9	41, M	112.6×10^9/L	89%	Yes	Yes	Acute monocytic leukemia	Diffuse large B cell lymphoma	[8]
10–15	55–94, 5 M, 1F	$40–199\times10^9$/L	N/A	Yes; 4/6 cases	Yes; 5/6 cases	Acute lymphoblastic leukemia (all 6 cases)	Blastoid mantle cell lymphoma	[9]

*37% in the bone marrow aspirate

lymphomas, one case of B-prolymphocytic leukemia, and one case of DLBCL.

Discussion

Here we describe a series of cases of B cell and T cell non-Hodgkin lymphomas that presented with clinical and peripheral blood findings suggestive of acute leukemia on preliminary examination at outside hospitals, the ED, or a local medical clinic. A primarily leukemic presentation is unusual for both aggressive B cell and T cell non-Hodgkin lymphomas. DLBCL, the most common aggressive B cell lymphoma, usually presents with nodal or extranodal lesions. Bone marrow involvement has been reported in 10–25% of cases, but peripheral blood involvement is rare [1]. Burkitt lymphoma typically involves extranodal sites, and may involve bone marrow, with or without circulating neoplastic cells. Patients may present with lymph node involvement, more often in adults than children. Rarely, patients may present with leukemia, with bone marrow and often CNS involvement [1]. The current case of Burkitt lymphoma (case 2) was initially thought to be acute lymphoblastic leukemia, based on the unusual presentation and blast-like morphologic appearance of the neoplastic cells in peripheral blood. HGBL, NOS, is a rare disease that typically presents with lymph node and extranodal involvement and advanced stage (Ann Arbor III/IV) disease, with bone marrow involvement reported in 34% of cases [10]. Leukemic involvement was not described in two large series of cases of HGBL, NOS (41 and 126 cases, respectively [10, 11]), so the presentation in our case (case 3) appears to be a rare occurrence. B-prolymphocytic leukemia is also a rare disease of mature B cells with no specific diagnostic immunophenotype [1]. The current case of B-prolymphocytic leukemia (case 5) was initially interpreted as acute leukemia, probably due in part to the rarity of the diagnosis, as well as the presence of significant leukocytosis and numerous cells in the peripheral blood that were mistaken for blasts. Peripheral T cell lymphoma, NOS, is the most common mature T cell neoplasm involving lymph nodes. Patients can present with advanced stage disease, with secondary involvement of bone marrow and other organs, including skin, but leukemic presentation is uncommon [1]. In our case (case 1), the rapidly rising white blood cell count, immature and pleomorphic appearance of the neoplastic cells, and skin involvement were initially interpreted as evidence of acute monocytic leukemia.

Considering the additional cases of non-Hodgkin lymphoma previously reported in the medical literature that presented as acute leukemia, all were subtypes that do not typically have a primarily leukemic presentation. Hepatosplenic T cell lymphoma may present with bone marrow involvement and cytopenias, but peripheral blood involvement at presentation is uncommon [1]. HGBL with *MYC* and *BCL2* or *BCL6* rearrangement (double hit lymphoma) typically presents with advanced stage disease, including involvement of lymphoid and extranodal sites, including bone marrow involvement, with peripheral blood involvement reported in 30% of cases [12]. Blastoid mantle cell lymphoma typically involves lymphoid tissue, and can involve spleen, bone marrow, extranodal sites, and peripheral blood [1]. Peripheral blood involvement can mimic chronic lymphocytic leukemia, prolymphocytic leukemia, or, uncommonly, acute lymphoblastic leukemia [1, 9].

Five of six patients with non-Hodgkin lymphoma that presented as acute leukemia at our institution received one of several multiagent chemotherapy regimens for their non-Hodgkin lymphoma, but, in general, the patients exhibited poor overall survival. All six of our patients exhibited extensive bone marrow involvement, 50% exhibited CSF involvement, and 50% exhibited lymph node involvement. Similarly, our literature review of patients with non-Hodgkin lymphoma that mimicked acute leukemia also revealed poor overall survival. In general, leukemic presentation of non-Hodgkin lymphoma has been associated with advanced stage disease, including bone marrow and extranodal site involvement, and poor prognosis [13–16], as noted in our patients. The mechanisms of lymphoma cell migration to the peripheral blood are unclear. One hypothesis is that this may be due to the differential expression of cell adhesion molecules on the surface of lymphoma cells, as has been noted in chronic lymphocytic leukemia versus mantle cell lymphoma [17]. In addition, *TP53* mutations are associated with advanced stage disease and poor prognosis in a number of non-Hodgkin lymphomas, including diffuse large B cell lymphoma, marginal zone lymphoma, mantle cell lymphoma, and Burkitt lymphoma [15, 18]. Interestingly, we found that *TP53* mutations were present in 4 of 6 of our cases non-Hodgkin lymphoma mimicking acute leukemia (cases 2, 3, 4, and 5), which may have contributed to the aggressive clinical courses noted in our patients. A complex karyotype has also been noted in cases of diffuse large B cell lymphoma presenting in leukemic phase [19], which may contribute to more aggressive clinical behavior; we found that 3 of 6 of our cases (50%) exhibited a complex karyotype.

One of the conclusions from the morphologic findings is that specific subtypes of aggressive non-Hodgkin lymphoma may exhibit a variable blast-like appearance in peripheral blood. For example, cases of DLBCL may have an acute monocytic leukemia-like appearance or a more undifferentiated blast-like appearance. Similarly, our case of peripheral T cell lymphoma, NOS, had an acute monocytic leukemia appearance, while Jelinek and Zuchnicka describe a case of peripheral T cell lymphoma, NOS, that had an acute lymphoblastic leukemia appearance in peripheral blood

[7]. Overall, it appears that the most common leukemic appearance of aggressive non-Hodgkin lymphomas is acute lymphoblastic leukemia-like morphology, followed by a more undifferentiated acute leukemia-like morphology unable to be further categorized based on morphologic findings. The finding that aggressive non-Hodgkin lymphomas may exhibit a blast-like appearance in peripheral blood, resembling acute myeloid leukemia or acute lymphoblastic leukemia, illustrates the importance of comprehensive immunophenotypic analysis in the initial diagnostic evaluation of hematolymphoid neoplasms. In all six of our cases, immunophenotypic analysis led to the correct identification of neoplastic, circulating, mature B cells or T cells, and a non-Hodgkin lymphoma diagnosis, following correlation with clinical, other laboratory, and radiologic findings.

In addition to rarely presenting initially in leukemic phase, cases of aggressive non-Hodgkin lymphomas may undergo a leukemic phase relapse, in which the neoplastic cells may have the morphologic appearance of acute leukemia. One case report described a 28-year-old woman with a history of DLBCL treated with multiagent chemotherapy, who presented with a 1 week history of fever and 5–8% circulating cells with a blast-like appearance, suspicious for acute leukemia. In addition, there was 30% bone marrow involvement, splenomegaly and abdominal lymphadenopathy. In that case, immunophenotyping confirmed the diagnosis of relapsed DLBCL [20]. Other subtypes of B cell non-Hodgkin lymphoma, such as follicular lymphoma, may rarely undergo a blast-like transformation several years after the initial diagnosis [18]. In a report of 5 patients with a history of follicular lymphoma, the patients exhibited a morphologic transformation involving peripheral blood, bone marrow, CNS, in one case, and lymphoid tissue, in two cases, to neoplastic cells having a blast-like appearance. Three cases analyzed were found to consist of mature B cells with monoclonal surface immunoglobulin light chain expression that were negative for CD34. All five cases were positive for follicular lymphoma marker BCL-2, negative for TdT, and positive for the follicular lymphoma-associated t(14;18) translocation [18].

Disease entities other than aggressive non-Hodgkin lymphoma may also mimic acute leukemia. Case reports describe a variety of non-hematolymphoid neoplasms presenting with an acute leukemia appearance, including rhabdomyosarcoma [21], small cell carcinoma [22], and malignant melanoma [23]. Recently, a patient with COVID-19 infection presented with transient pancytopenia and increased blasts in the peripheral blood [24]. Patients with nutritional deficiencies, such as vitamin deficiencies, may present with findings that resemble acute leukemia [25]. In addition, patients with toxic insults to the bone marrow as a result of drug or alcohol abuse may exhibit transiently increased blasts resembling acute leukemia upon withdrawal of the toxic substances [26]. These cases, along with the aggressive non-Hodgkin lymphoma cases that we and others described, emphasize the importance of comprehensive immunophenotypic analysis, as well as correlation with other clinical, laboratory, and radiologic findings, in order to arrive at the correct diagnosis.

Author contribution Both authors designed the study, analyzed the data, contributed to the manuscript preparation, and approved the final version of the manuscript for submission.

Declarations

Conflict of interest The authors declare no competing interests.

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