


# Rare but Potentially Fatal Presentations of Diffuse Large B-cell Lymphoma: Leukemic Phase or Hemophagocytic Syndrome in Bone Marrow

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**ABSTRACT:** Diffuse large B-cell lymphoma (DLBCL) is a type of non-Hodgkin Lymphoma commonly presenting as a solid tumor either by nodal or extra-nodal manifestations. Here we describe two atypical presentations of lymphoma, finally resulting in the diagnosis of DLBCL. Case 1: A 53-year-old man with a previous history of nasopharyngeal carcinoma presented with a two-week history of B-symptoms and hyperleukocytosis. Peripheral blood film showed 78% abnormal mononuclear cells. Immunohistochemical stain showing Ki-67 of 90%, negative c-myc, BCL2 and BCL6, and negative c-MYC with fluorescence in-situ hybridization studies on the trephine biopsy, concluded the diagnosis of CD5+ DLBCL of ABC subtype. He received intravenous cyclophosphamide and oral prednisolone for cytoreduction, followed by 6 cycles of chemo-immunotherapy. However, he succumbed due to severe sepsis after the completion of therapy. Case 2: A 56-year-old lady who was initially investigated for pyrexia of unknown origin was noted to have hemophagocytosis upon bone marrow aspirate examination. The bone marrow trephine biopsy revealed some atypical clusters of B-cells positive for CD20 which was inconclusive. PET-CT scan noted an enlarged hypermetabolic spleen without lymphadenopathy. Splenic biopsy with immunohistochemical studies revealed DLBCL of ABC subtype. The diagnosis was consistent with primary splenic DLBCL. She became unwell post splenic biopsy and was admitted to the intensive care unit where she passed away 2 weeks later from *Candida* and *Sternotrophomonas* septicemia. These cases highlight the atypical presentations of a common subtype of NHL in our center. Arriving at the definitive diagnosis can be difficult especially when patients are acutely ill, hampering the necessary invasive procedures for diagnosis. The outcomes of both cases are briefly discussed hoping to spread awareness among clinicians on the rare and acutely critical presentations of DLBCL.

**KEYWORDS:** Diffuse large B-cell lymphoma, leukemic phase, hemophagocytic syndrome

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## Introduction

DLBCL is an aggressive mature B-cell lymphoma under the umbrella of NHL classification and immunophenotypically heterogeneous. About 31% of all NHLs in western countries are classified as DLBCL, which also comprises 37% of all B-cell tumors worldwide.<sup>1</sup> The revised 2017 World Health Organisation (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues has classified this disease further, with the inclusion of genetic abnormalities, in line with the advancement of molecular medicine.<sup>2</sup> Confirmation of the diagnosis is made by histopathological examination of the tissue, consisting of a host of immunohistochemistry (IHC) panels, with the addition of molecular techniques if the diagnosis is doubtful. Further classification for prognostic purposes consists of subtyping the disease into the germinal center (GCB) or activated B-cell (ABC) subtypes, for which Han's algorithm has been widely used.<sup>3</sup> Clinically, the disease has been described as classically presenting as a rapidly enlarging mass anywhere within the body,

with or without B-symptoms.<sup>2</sup> Due to the wide range of clinical presentations in nodal or extra-nodal tissues, this disease manifests itself with various symptoms and signs, the least being acute leukemia or hemophagocytic syndrome, which are rare but potentially lethal conditions in the acute setting. Recognizing these rare but potentially lethal presentations is critical in arriving at the correct diagnosis and initiating chemotherapy promptly before patients deteriorate.

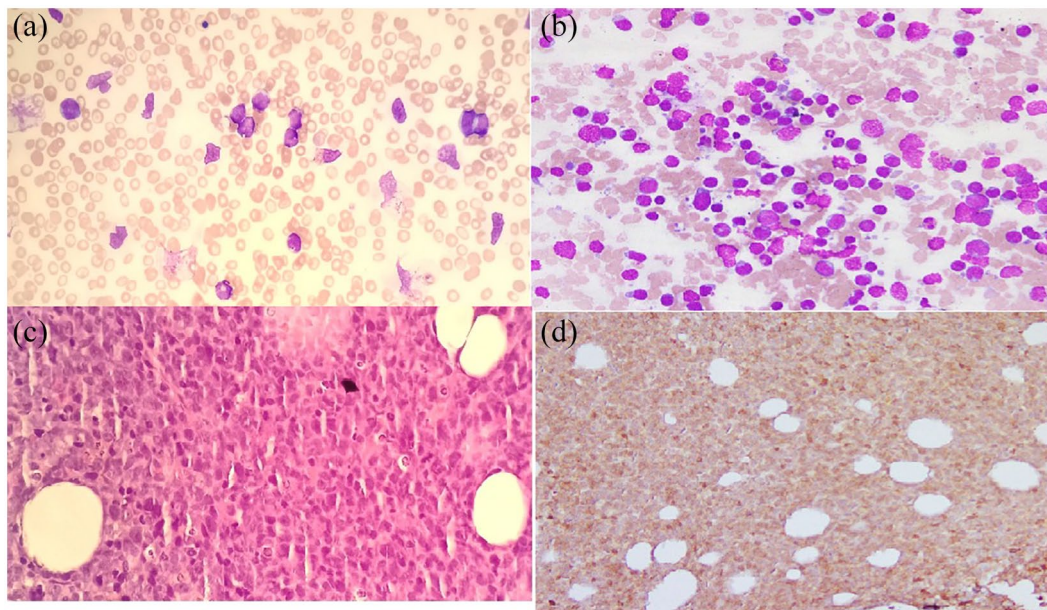
## Case Presentation

### *Case 1: DLBCL presenting in leukemic phase*

A 53-year-old man with a history of nasopharyngeal carcinoma three years before presentation, presented with a two-week history of low-grade fever, loss of appetite, loss of weight, lethargy, and pedal edema. Previously, in 2016, he completed chemoradiotherapy and was disease-free up to this presentation. Clinically, he was in septic shock with the presence of shotty cervical lymph nodes with hepatosplenomegaly. Complete blood count (CBC) showed a hemoglobin (Hb) level of 7.2 g/dL, white blood cell (WBC) count of

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**Figure 1.** Photomicrograph of (a) peripheral blood film showing abnormal mononuclear cells with heterogeneous morphology. Some are vacuolated while some had prominent nucleoli resembling blasts (May Grunwald-Giemsa (MGG), 40x magnification); (b) Hypercellular bone marrow aspirate with a predominant lymphoid cell of small to large sizes (MGG, 40x magnification); (c) Trephine biopsy showing total displacement of hematopoietic elements with small to moderate size, malignant lymphocytes. (H&E, 20x magnification); (d) The lymphoid cells immunohistochemistry with positive for CD5 (CD5 staining, 20x magnification).

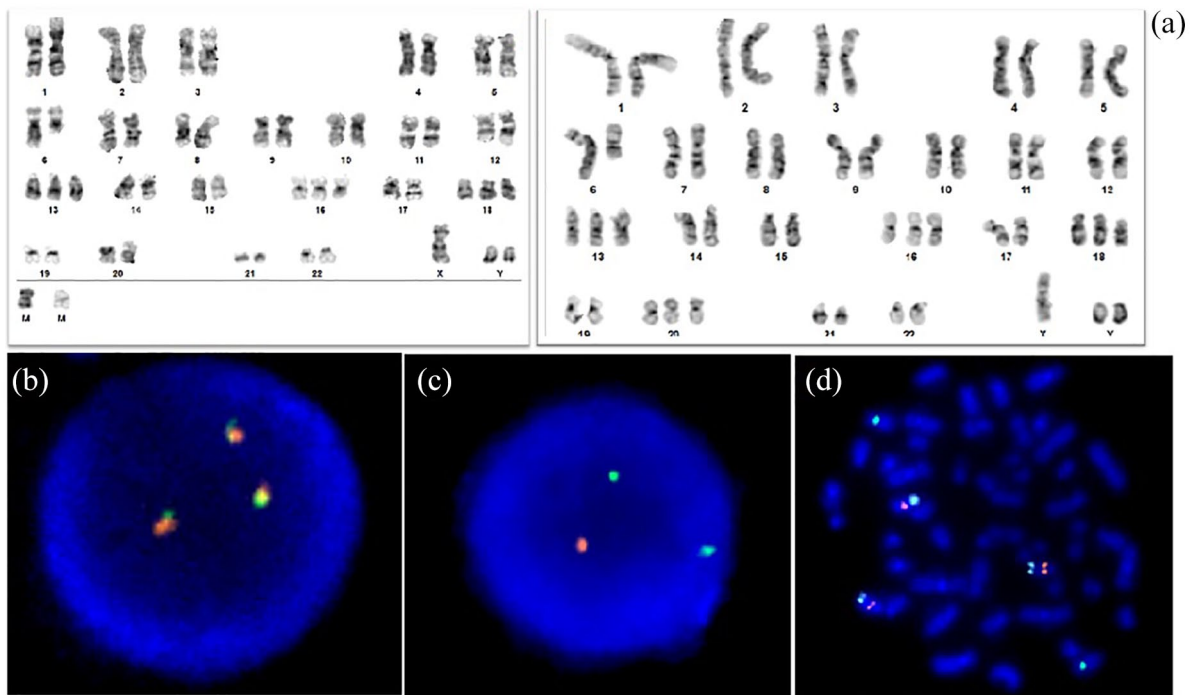
$166.2 \times 10^9/L$ , and platelet count of  $45 \times 10^9/L$ . The absolute neutrophil count was  $4.3 \times 10^9/L$ . The lactate dehydrogenase (LDH) level was  $>8465 U/L$  (normal range: 125–220 U/L). There were no signs of hyperviscosity syndrome. He was immediately commenced on intravenous tazobactam/piperacillin and hydration support for hyperleukocytosis.

Acute leukemia was immediately suspected and an urgent peripheral blood film showed a leucoerythroblastic picture with 78% abnormal mononuclear cells. The cells are small to moderate in size with bluish, large to moderate cytoplasm, some with high nuclear-to-cytoplasmic ratio resembling blasts with prominent nucleoli and vacuolated cytoplasm. Many smudge cells were also noted (Figure 1a). The bone marrow aspirate was markedly hypercellular with infiltration by lymphoid cells similar in morphology to the peripheral blood (Figure 1b). Immunophenotyping by flow cytometry showed abnormal B-lymphoid population gated at low SSC/bright CD45 area and expressed CD20, CD19, CD5, CD22 (dim), CD200, BCL-2, and with Kappa light chain restriction. The cells were negative for CD 34, TdT, CD 10, CD 23, CD 3, and FMC-7. The differential diagnosis of CD5+ B-lymphoproliferative disease (LPD) was made.

He required ionotropic support for five days, but his condition improved with antibiotics. He was started on intravenous cyclophosphamide and oral prednisolone for initial cytoreduction, because of the high risk of tumor lysis syndrome. Staging by Positron Emission Tomography and Computed Tomography (PET-CT) noted diffuse, hypermetabolic marrow with cervical, axillary and inguinal node involvement, consistent with

stage IV disease. Histopathological results from the bone marrow trephine biopsy showed total displacement of hematopoietic cells (Figure 1c) with heterogeneous sizes of lymphoid cells and positive for CD20, CD5 (Figure 1d), BCL-2, and MUM-1. They were negative for CD10, CD 23, cyclin D1, c-myc, and BCL-6. The negative cyclin D1 ruled out mantle cell lymphoma. Ki-67 proliferative index was more than 90% and fluorescence in situ hybridization (FISH) study for c-MYC rearrangement was negative, ruling out the diagnosis of Burkitt's lymphoma. The IHC profile and FISH results did not meet with the high-grade lymphoma profile, and the diagnosis of CD5+ DLBCL of ABC subtype was made. Cytogenetics studies from bone marrow aspirate showed  $52, XYY, del(6)(q22), +13, +16, +18, +2mar[3]/51, XYY, del(6)(q22), +13, +16, +18, +20[2]$  which is compatible with complex karyotype (Figure 2a). FISH analysis from the bone marrow aspirate showed evidence of 3 copies of CBFB (16q22) region in 87% of cells (Figure 2b), deletion of p53(17p13.1) locus in 36% of cells (Figure 2c), and 3 copies of D13S319 (13q14.3) and 13q34 region in 80% of cells (Figure 2d). The left cervical lymph node from Tru-cut (Merit Medical, South Jordan, UT, USA) biopsy revealed atypical lymphoid cells.

He was then commenced on chemoimmunotherapy consisting of dose-adjusted rituximab, etoposide, vincristine, doxorubicin, prednisolone, and cyclophosphamide (DA R-EPOCH) with a plan for hematopoietic stem cell transplantation, given a relatively young age and aggressive disease with Revised International Prognostic Index (R-IPI) score 3. He achieved



**Figure 2.** Cytogenetic analysis of G-banded chromosomes for cultured bone marrow showing (a) presence of 2 cell lines, 52,XYY,del(6)(q22),+13,+16,+18,+2mar in 3 metaphase cells (left) and 51,XYY,del(6)(q22),+13,+16,+18,+20 in 2 metaphase cells (right). Bone marrow aspirate FISH analysis using (b) Vysis CBFβ break apart FISH probe kit showing the presence of 3 copies in the interphase cells; (c) Vysis LSI p53/LSI ATM probe a deletion of p53 (1 orange signal) in the cells; and (d) Vysis LSI D13S319/LSI 13q34/CEP 12 Multi-color Probe Set showing 3 copies of chromosome 12 (orange and green signals) and 2 normal copies of chromosome 12 (single green signal) in the metaphases.

partial remission based on the PETCT results after 3 cycles of DA R-EPOCH. However, he passed away after the sixth cycle due to severe neutropenic sepsis.

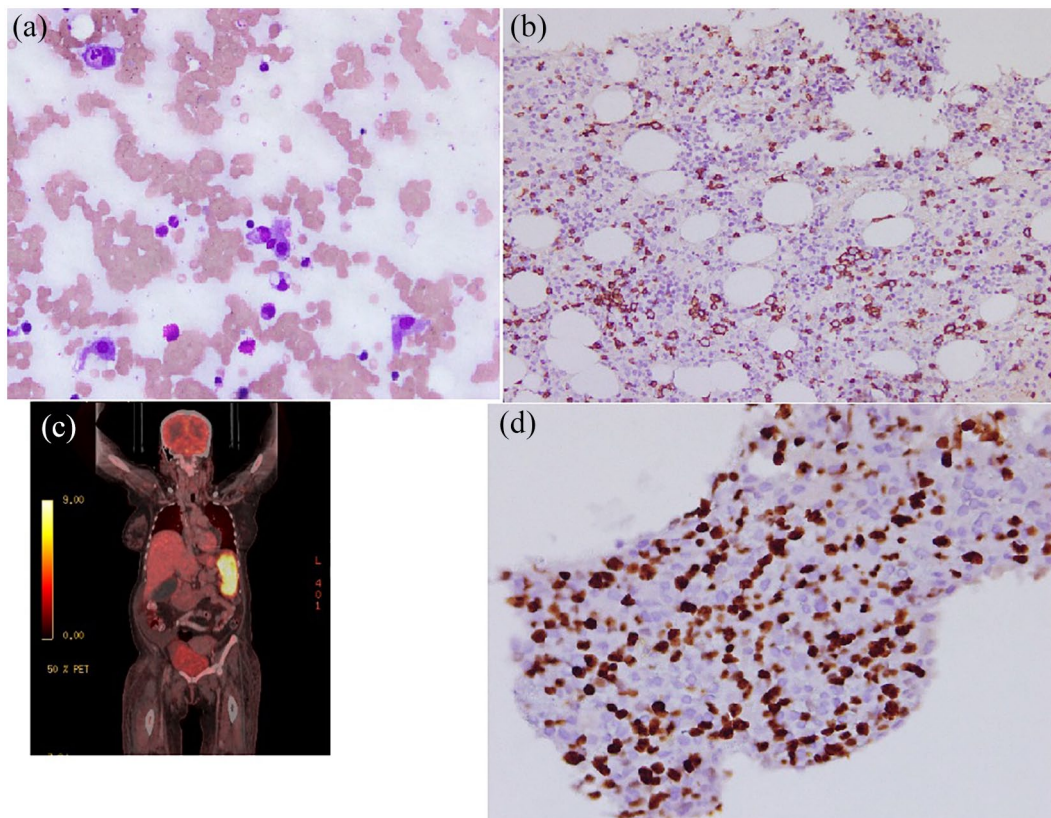
### Case 2: DLBCL presenting as hemophagocytic syndrome

A 52-year-old woman with underlying diabetes, hypertension, and dyslipidemia presented to our hospital with a two-week history of high-grade fever. Clinical examination showed normal findings. CBC showed a Hb level of 7.7 g/dL, WBC count of  $8.4 \times 10^9/L$ , and platelet count of  $323 \times 10^9/L$ . C-reactive protein was 12.07 mg/L. Repeated infectious disease work-up, including blood, urine, and sputum cultures were negative. A diagnosis of pyrexia of unknown origin was made and she was initially started on broad-spectrum antibiotics. Cardiac echocardiography showed no vegetations on any of the cardiac valves. Serological investigations showed no evidence of active Epstein Barr virus (EBV), cytomegalovirus (CMV), herpes simplex, Hepatitis B, Hepatitis C, VDRL, and HIV. Fever persisted despite multiple courses of antimicrobials. Interestingly, peripheral blood film showed severe anemia with red cell agglutination, suggestive of cold autoimmune hemolytic anemia with a Coomb's test positive for IgG. Serum bilirubin, however, was normal at 10.8 mmol/L, but LDH was high at 844 U/L. This was later found to be due to a rare anti-Sda antibody.

However, her anemia persisted despite multiple transfusions with no remission of temperature spikes and platelet counts dropped progressively to  $65 \times 10^9/L$ . Computed tomography (CT) of the thorax, abdomen, and pelvis at Day 8 of admission showed enlarged liver of 17 cm and non-specific mesenteric streakiness at the right lower abdomen, which could be due to ongoing infection or inflammation. Spleen size was normal. There was also localized fluid surrounding the right ovary, which was reported as physiological. Evidence of diverticular disease was also present, with no signs of acute diverticulitis. On Day 15 of admission, diagnosis of HLH was confirmed based on persistent fever, presence of cytopenias (Hb 5.7 g/dL, WBC  $3.8 \times 10^9/L$  and platelet counts  $65 \times 10^9/L$ ), ferritin level of  $>40000 \mu\text{g}/L$ , hypertriglyceridemia of 2.67 mmol/L, LDH 1550 U/L, and bone marrow aspirate findings of histiocytic hyperplasia with increased hemophagocytic activities (Figure 3a). No increase in plasma cells or lymphocytes. Trepine biopsy showed scattered small clusters of moderate-sized B-cells positive for CD20 (Figure 3b). The cells expressed a low Ki-67 index and negative for CD10, BCL-2, BCL-6, and MUM-1. The clinical significance of the B-cell clusters was not ascertained and diagnosis of lymphoma was not considered.

She was treated with high-dose dexamethasone, intravenous antibiotic, and antifungal therapies. Her condition improved temporarily but two weeks later, she developed high-grade fever again. PET-CT scan performed at Day 40 of





**Figure 3.** (a) Photomicrograph of bone marrow aspirate of the patient showing histiocytes engulfing other hematopoietic cells (MGG, 40x magnification); (b) trephine biopsy showing the scattered distribution of lymphoid cells positive for CD 20. (CD20 immunostain, 20x magnification), (c) Coronal view of PETCT scan showing diffusely hypermetabolic (SUVmax: 11.3) enlarged spleen (14.8 cm), and (d) splenic biopsy showing infiltration by malignant lymphoid cells with a Ki-67 index of 60% (Ki-67 immunostain, 40x magnification).

admission scan revealed an enlarged and diffusely hypermetabolic spleen (Figure 3c) without evidence of disease elsewhere. Subsequently, a splenic biopsy was performed two days later but she deteriorated about four hours after the biopsy, requiring intubation and transfer to the intensive care unit. Histology of the splenic tissue showed diffuse infiltration by neoplastic lymphoid cells positive for CD20, CD79 $\alpha$ , and MUM-1, while the Ki-67 index was 60% (Figure 3c). These cells were negative for CD 3, CD 68, CD 10, CD 21, and BCL-6, consistent with DLBCL of ABC subtype. She succumbed at D57 of admission after developing severe hospital-acquired *Candida* and *Sternotrophomonas* septicemia resulting in septic shock and multiorgan failure.

### Discussion

DLBCL is a heterogeneous group of disorders with variable histological and clinical behaviors. It is characterized morphologically by large, atypical, lymphoid cells with the appearance of pale blue cytoplasm, nuclei that are round, irregular, and vesicular with prominent nucleoli, and relatively abundant cytoplasm.<sup>4</sup> DLBCL is the most common of NHL; however, presentations of hemophagocytic lymphohistiocytosis (HLH) or leukemic phase are unusually observed among DLBCL cases.

Case 1 had bone marrow disease at presentation, with cervical, axillary, and inguinal nodes involvement, consistent

with stage IV disease and IPI score 3 denoting poor prognosis. With the differential diagnosis of acute lymphoblastic leukemia, this case highlights the importance of the application of flowcytometric immunophenotyping to distinguish acute leukemia from NHL in the blastic phase. Bone marrow infiltration by neoplastic circulating cells may occur in lymphomas, such as in leukemia, leading to a leukemic phase.<sup>4</sup> A leukemic phase is usually seen as a progressive phase or in stage IV disease and is rare in DLBCL at the time of diagnosis.<sup>5,6</sup> Lymphomas are usually diagnosed based on morphology and immunophenotypic findings; however, the overflow of these lymphoma cells into the circulation can be diagnosed from cellular immunophenotype analysis by flow cytometry. Interestingly, the immunophenotyping results in Case 1 demonstrated a positive expression of CD5 with notably complex cytogenetics including p53 deletion.

CD5+ DLBCL is a subset of DLBCL with distinct clinicopathological features and only represents up to 10% of DLBCLs.<sup>7,8</sup> The majority of CD5+ DLBCL cases are of the activated B cell subtype (ABC) of DLBCL.<sup>9</sup> In the literature, patients with CD5+ DLBCL are more likely to be older and female, with high LDH, B symptoms, extra-nodal involvement, poor performance status (PS), more frequent CNS involvement, and advanced clinical stage.<sup>8,10-12</sup> Zhao et al reported that patients with p53 and CD5 co-expression had the worst

progression free survival (PFS) and overall survival (OS). CD5+ DLBCL has a higher prevalence of p53 overexpression, and CD5 enhances the negative effect of p53 overexpression in DLBCL.<sup>11</sup> Our patient presented with poor prognostic markers including leukemic phase, advanced clinical stage, high IPI score, and CD5+ expression and p53 deletion. He achieved partial remission following 3 cycles of DA R-EPOCH, but the end of treatment assessment was not performed as he succumbed to severe neutropenic sepsis. Miyazaki et al<sup>13</sup> reported complete response rate was 91%, in a Japanese cohort of 49 patients with an overall response rate of 94%.

Our second case presented with secondary HLH, which is a clinical syndrome characterized by a hyperinflammatory condition, resulting in increased cytokine production, impaired cytotoxic T and NK cell production, and stimulation of mononuclear cells. The diagnosis of HLH is challenging due to its rare occurrence. She had a prolonged, high-grade fever ranging from 38°C to 40°C, anemia, thrombocytopenia, splenomegaly, hypertriglyceridemia, hyperferritinemia, and raised LDH. Given these abnormal parameters, bone marrow and trephine aspiration were performed which was suggestive of HLH. H score was used for diagnostic criteria, consisting of 10 variables designed to estimate an individual's risk for HLH. Our patient fulfilled 6 of 8 criteria and had an H score of 235, making the probability of HLH 98%.

HLH is a rare and overwhelming clinical syndrome due to abnormal immune activation. The reasons for this immune dysregulation vary and the syndrome is categorized as either primary (familial) or secondary (acquired). Primary HLH typically presents in the first year of life with or without a positive family history. It is a recessive condition caused by mutations in genes important for NK and T-cell granule-mediated cytotoxic function.<sup>14</sup> Secondary HLH is seen in adults, usually caused by triggers such as viral infections, malignancy, or autoimmune processes. These disorders are clinically characterized by excessive systemic production of inflammatory cytokines leading to macrophage activation, hemophagocytosis, pancytopenia, hepatosplenomegaly, lymphadenopathy, fever, seizure, or central nervous system complications, capillary leak with pulmonary insufficiency, hypotension, and renal failure. HLH can occur as the initial presentation of the underlying disorder or later in the course, occasionally in the setting of disease progression or the addition of a trigger.<sup>15</sup> Lymphoma is the most common cause of malignancy-related HLH and accounts for 27% of secondary HLH. DLBCL comprised the largest defined subtype at 11%.<sup>16</sup> The treatment of HLH is aimed to halt any underlying triggers and control the overactive immune system. If a malignancy or infection is identified, disease-specific treatment should be initiated immediately.<sup>16</sup> Upon diagnosing HLH, dexamethasone was commenced in Case 2 to control the overactive immune system while investigating the etiology of HLH.

As the histopathological findings of the spleen confirmed DLBCL and the absence of significant lymphadenopathy, a

diagnosis of primary splenic DLBCL was concluded. Splenic involvement can be part of diffuse dissemination of the lymphoma, however, the spleen itself may be the primary site. Dasgupta et al. defined primary splenic lymphoma as lymphoma involving the spleen only, along with the involvement of lymph nodes confined to the splenic hilum.<sup>17</sup> Primary splenic lymphoma (PSL) is a rare tumor with an overall incidence of less than 1% of the tumors occurring in the spleen.<sup>16-18</sup> According to Skarin et al,<sup>19</sup> diagnosis of PSL can be made if in any lymphoma, and if splenomegaly is the predominant feature. So far, there is a scarcity of reported cases of newly diagnosed PSL presenting with HLH that has been described in the literature. Han et al reported a 77-year-old man with PSL presenting with HLH who developed spontaneous splenic rupture that occurred after chemotherapy.<sup>16</sup> He responded well to chemotherapy and achieved complete remission.<sup>16</sup>

The presence of HLH greatly increases the difficulty of diagnosing PSL. Eradication of the underlying disease is the cornerstone of HLH treatment. Case 2 highlights the need for a high index of suspicion for HLH. When constructing the differential diagnoses of a patient with prolonged fever, cytopenia, liver derangement, and elevated ferritin and LDH, it is paramount to consider hemophagocytic lymphohistiocytosis as a possible etiology. Aggressive courses of immunosuppressants and anti-inflammatory agents (such as glucocorticoids) are used to control widespread inflammation. Retrospectively, the second case may have benefited from HLH-specific therapy (ie, NHL chemotherapy) early after the presentation. The mortality rate of HLH without treatment is high and HLH patients with associated malignancy suffer worse prognosis.<sup>20</sup> Treatment is both supportive and definitive and targeted at the specific underlying condition (ie, specific treatment for malignancy).

## Conclusion

These cases highlight the atypical presentations of DLBCL in our center. Arriving at the definitive diagnosis can be difficult, especially when patients are acutely ill, therefore hampering the necessary invasive procedures for diagnosis. The outcomes of both cases are briefly discussed in the hope to increase awareness among clinicians of the rare and acutely critical presentations of DLBCL.

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## Author Contributions

WAWMZ and AZI collected data and drafted the manuscript; AZI, NY, AI, NM, and SS provided the photomicrographs with descriptions; NY, SP, and NRT helped review the

manuscript and provided feedback for improvement. All authors have read and approved the manuscript.

### Availability of Data and Materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.


### Ethical Approval

Ethical approval was not sought for the present case report because it is not required as per university guidelines. This study was completed per the Declaration of Helsinki.

### Informed Consent

Written informed consent was obtained from legally authorized representatives before the study.

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