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LETTER TO THE EDITOR

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Leukemic presentation with discordant morphology in triple-hit lymphoma—A diagnostic pitfall during COVID-19 pandemic

Dear Editors,

As the pandemic rears on, virological testing for COVID-19 in all patients prior to each invasive procedure becomes logistically demanding in resource-poor settings. Invasive diagnostic procedures are thus often being avoided if adequate information can be gleaned from noninvasive tests. However, deviation from well-established investigative algorithms may lead to unnecessary diagnostic confusion with potentially serious consequences, as we discovered in the case described below.

A 33-year-old man presented with pain abdomen, loss of appetite, weight loss, and generalized lymphadenopathy for 3 months. Abdominal imaging showed conglomerated retroperitoneal lymph-nodal mass and intestinal mural thickening. Complete blood count revealed anemia and leukocytosis (hemoglobin-99 g/L; total leucocyte count-42.6 $\times$ 10^9/L; platelet count-342 $\times$ 10^9/L). Peripheral blood (PB) smear examination revealed lymphocytosis (absolute lymphocyte count-33.6 $\times$ 10^9/L) with small- to intermediate-sized, centrocyte-like cells having irregular nuclear contour and markedly cleaved nuclei (Figure 1A-C). This finding of abnormal lymphocytes on PB prompted us to proceed with immunophenotyping and subcategorization of the lymphoma using the PB sample itself, and invasive biopsy procedures were avoided/postponed considering a recent surge of COVID-19 cases in our locality.

Flow-cytometric analysis (Figure 1D-G) detected kappa light-chain restricted clonal B-cells expressing CD45, bright CD20, CD19, dim CD38, dim CD10, CD200 and CD79b. These clonal B cells did not express CD5, CD23 or CD43. Follicular lymphoma was provisionally diagnosed based on lymphocyte morphology and

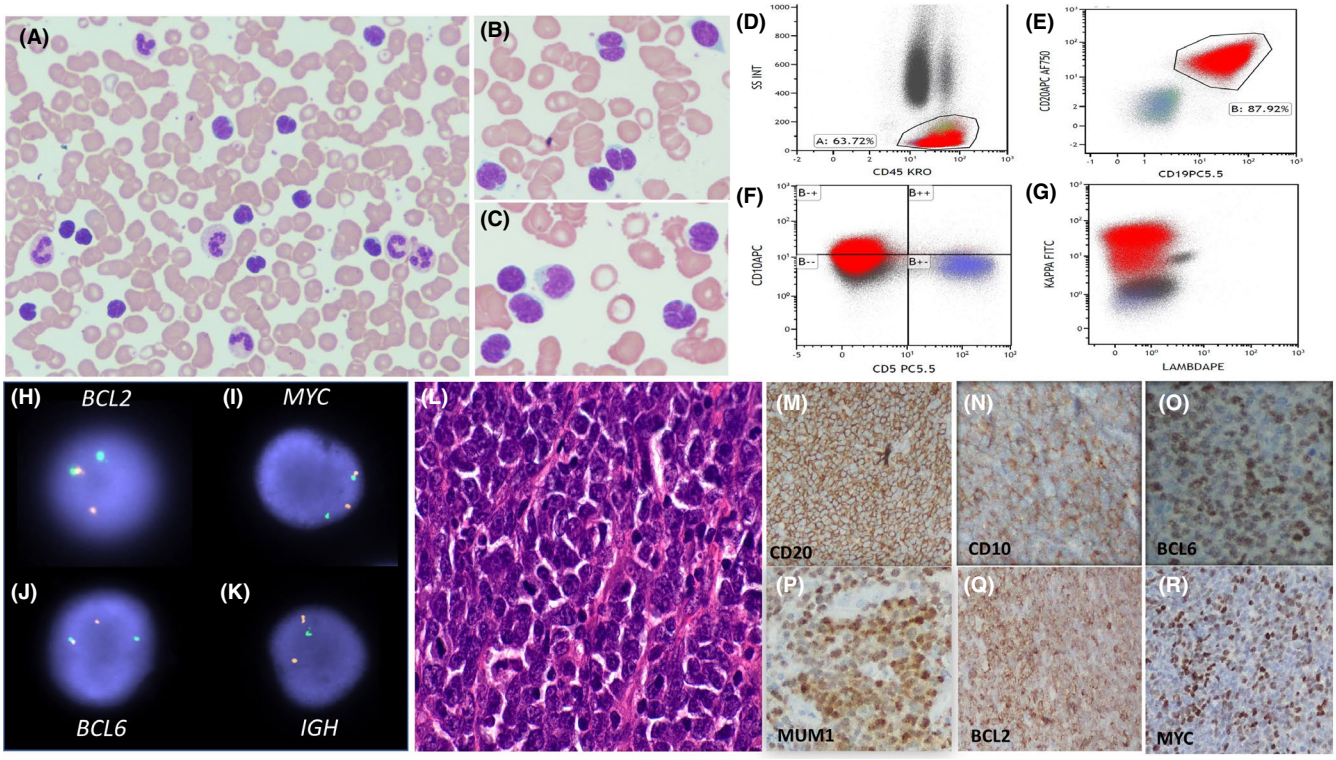

FIGURE 1 A-C, Peripheral blood smear showing lymphocytosis, with small-to medium-sized centrocyte-like lymphocytes showing nuclear cleaving; D-G, flow cytometric immunophenotyping of the gated lymphocytes showing positivity for CD19, CD20, and CD10 (dim), negativity for CD5, and kappa restriction; H-K, FISH using dual-color break-apart probes showing *BCL2*, *MYC*, *BCL6*, and *IGH* (bi-allelic) rearrangements; L, lymph node biopsy showing sheets of intermediate-to large-sized atypical lymphoid cells and frequent mitotic figures (Hematoxylin & Eosin; 40x); M-R, immunohistochemistry showing the atypical lymphoid cells to be positive for CD20, CD10, BCL6, MUM1, BCL2, and MYC

immunophenotypic findings. Remarkably, fluorescence in situ hybridization (FISH) using dual-color break-apart probes (Vysis; Abbott Inc) performed on the PB lymphocytes (Figure 1H-K) showed *MYC*, *BCL2*, and *BCL6* rearrangements. Together with bi-allelic *IgH* translocation, a working diagnosis of triple-hit lymphoma was offered. At this juncture, the diagnostic entities considered were (i) triple-hit follicular lymphoma (TFL) or (ii) high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBL-DH/TH) showing discordant PB morphology, both of which are rare entities. To resolve the diagnostic confusion, it was ultimately decided to obtain biopsy from a cervical LN. Nodal architecture was effaced by sheets of intermediate to large-sized atypical lymphoid cells with high N:C ratio, coarse chromatin, and prominent nucleoli. Large areas of necrosis, frequent mitotic, and apoptotic figures were also observed (Figure 1L). On immunohistochemistry, these atypical cells showed diffuse positivity for CD20, CD10, BCL6, MUM1, BCL2, and MYC (>40% cells) and were negative for CD3, cyclin D1, and CD30 (Figure 1M-R). These histological features together with the FISH findings clinched the diagnosis of HGBL-DH/TH, with a discordant morphology in PB.

HGBL-DH/TH is a newly defined entity in the 2016 World Health Organization classification of hematolymphoid tumors. It constitutes 1%-12% of tumors with diffuse large B-cell morphology.[1] Recognition of this relatively rare entity is important because of its aggressive disease course and treatment refractoriness.[2] R-EPOCH regimen is preferred in HGBL-DH/TH due to superior complete response rate compared with R-CHOP and due to less toxicity than other intensive chemotherapies.[2,3] Our patient had a leukemic blood picture. Although well described in various non-Hodgkin lymphomas, leukemic presentation is extremely unusual in HGBL-DH/TH.[4] The differential diagnosis considered in our case prior to LN biopsy was TFL, a rare entity with around 40 cases reported in literature. TFL shows histological features of follicular lymphoma without the areas of high-grade cytological transformation; however, cytogenetic testing reveals *MYC* and *BCL2* and/or *BCL6* rearrangements.[5] The evolution of HGBL-DH/TH from a pre-existing follicular lymphoma was a possibility that could not be explored completely in this case.

With increasing COVID-19 cases, our hospital guidelines mandated avoiding close, lengthy patient interactions whenever possible, without hampering patient care. Heeding this, we attempted to diagnose our case on PB, but the diagnostic confusion arose due to discordance of PB morphology with FISH findings. Eventually, it was LN histology, the established modality for lymphoma diagnosis, that came to our rescue. Morphologic variation of neoplastic infiltrates in different biopsy sites is a well-documented phenomenon in lymphomas.[6] In most cases, discordance is documented as small cell morphology in PB and/or bone marrow as opposed to large cell predominance in LN biopsy.[6-8] However, such discordance in HGBL-DH/TH is extremely unusual and, to the best of our knowledge, has not been previously reported in literature. The clonal relationship between these discordant populations also needs further elucidation.[9,10] Our case highlights the need for complete diagnostic work-up, even in these trying times, to avoid unnecessary dilemmas. Needless to say, all procedures should be performed with adequate personal protective measures.

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None.

CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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