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B-CELL LYMPHOMA, UNCLASSIFIABLE, WITH FEATURES INTERMEDIATE BETWEEN DIFFUSE LARGE B-CELL LYMPHOMA AND CLASSICAL HODGKIN LYMPHOMA WITHOUT MEDIASTINAL DISEASE: 4 CASES

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B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between Diffuse Large B-Cell Lymphoma and Classical Hodgkin Lymphoma Without Mediastinal Disease: 4 Cases
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ABSTRACT
B-cell lymphoma, Unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, is usually discussed primarily as a mediastinal tumour. Authors have acknowledged that non-mediastinal cases can occur, but their features are not described in detail. Studies have shown some clinical (age) and genetic differences between mediastinal and non-mediastinal cases, but survival is similar. Recently, it was proposed that the name not change, but that two subtypes be distinguished as mediastinal and non mediastinal. Here, we report 3 nodal and 1 extranodal involvement cases of unclassifiable B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma with no evidence of mediastinal disease.

Keywords: gray zone, lymphoma, non mediastinal

INTRODUCTION
In recent years, cases with morphological and immunophenotypic features transitional between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (CHL) have been reported. These cases, initially referred to as “gray zone lymphomas,” were assigned in the 2008 WHO classification to a provisional category designated as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL (BCLU-DLBCL/CHL)[1]. BCLU-DLBCL/CHL usually presents with mediastinal manifestations and overlapping clinical, morphological, and immunophenotypic features of DLBCL and CHL, especially primary mediastinal large B-cell lymphoma (PMBCL) and nodular sclerosis CHL [2]. It also includes occasional cases involving non-mediastinal lymph node sites [1]. Studies have shown some clinical (age) and genetic differences between mediastinal and non-mediastinal cases, but survival is similar [3]. Recently, it was proposed that the name not change, but that two subtypes be distinguished: mediastinal and non mediastinal [4]. Similar to CHL, they are less common in African and Asian populations [1]. Here, we report four cases of BCLU-DLBCL/CHL three with nodal and one with extranodal involvement and no evidence of mediastinal disease.

CASE 1
A 36-year-old man presented with a left axillary lymphadenopathy. Computed tomography (CT) examination did not reveal any mediastinal tumor. Excision biopsies of left axillary lymph nodes were performed and the lymph node exhibited a nodular growth pattern with fibrous bands and showed variable sheet like, confluent growth of Reed–Sternberg like (HRS-like) cells and lacunar cells. The inflammatory infiltrate was prominent with many lymphocytes and histiocytes, but fewer eosinophils and sparse plasma cells observed (Figure 1A). On immunohistochemical (IHC) staining, the HRS-like cells and lacunar cells expressed variable staining for CD30, CD15 and CD45, but diffuse and strongly staining for CD20 (Figure 1B) and PAX5. Moreover, negativity for CD79a (Figure 1C) and ALK-1 were noted. Immunohistochemistry for Epstein-Barr virus (EBV), LMP1 and in situ hybridization (ISH) for EBV encoded RNA (EBER) yielded negative results. The other immunohistochemical features, OCT-2 and BOB.1, were also variably stained. These findings indicate an intermediate character between CHL and DLBCL, and therefore, we diagnosed the patient as BCLU-DLBCL/CHL.

CASE 2
A 27-year-old woman was referred with a recent finding of anaemia. She also complained of B symptoms. A CT scan demonstrated left axillary lymphadenopathy and left mammary tumour, but revealed no mediastinal tumour. There was no tonsillar enlargement and splenomegaly. The trephine biopsy of bone marrow showed the proliferation contained many histiocytes, fewer small lymphocytes and sparse plasma cells, eosinophils and neutrophils with many large atypical cells consistent with HRS cells and some variants in diffusely fibrous stroma (Figure 2A). IHC staining was strongly positive for CD30 and CD20 (Figure 2B) in the malignant Hodgkin’s and HRS cells. But they did not demonstrate CD15, CD45, CD79a (Figure 2C) and ALK-1 positivity. Immunohistochemistry for EBV (LMP1) and ISH for EBER were positive. OCT-2, BOB.1 and CD23 were negative. These results represent a mixture of features of both CHL and DLBCL. We diagnosed the patient as BCLU-DLBCL/CHL.

CASE 3

An 11-year-old man presented with a history of right cervical lymphadenopathy. CT scan demonstrated right cervical lymphadenopathy, but revealed no mediastinal tumour. Excision biopsies of left axillary lymph nodes had many Hodgkin’s and HRS cells with many reactive lymphocytes and histiocytes surrounding but no plasma cells, eosinophils and neutrophils were seen (Figure 3A). Immunohistochemically, Hodgkin’s and HRS cells were strongly positive for CD30, CD20 (Figure 3B) and Pax5 but they were negative for CD45, CD15, CD79a (Figure 3C) and Alk1. EBV (LMP1) and ISH (EBER) were also positive. Additionally CD23 was negative. These findings indicated an intermediate character between CHL and DLBCL. We diagnosed the patient as BCLU-DLBCL/CHL.

CASE 4

A 65-year-old man presented with inguinal and intra abdominal lymphadenopathies. Excision biopsy of the inguinal lymphadenopathies showed sheet-like, confluent growth of pleomorphic tumour cells with many reactive lymphocytes and histiocytes surrounding, fewer eosinophils and neutrophils and sparse plasma cells (Figure 4A). The variation in cytological features ranged from medium to large cells with clear cytoplasm resembling centroblasts, whereas others resembled classical HRS cells; all were intimately associated with a diffuse and coarse fibrotic stroma. Neoplastic cells were strongly positive for CD20 (Figure 4B) and PAX5, variably positive for CD30 and CD79a (Figure 4C) but negative for CD45 and ALK-1. Immunohistochemistry for EBV (LMP1) were negative, but ISH for EBER were patchily positive in the HRS cells. The tumour showed marked variation of morphological and IHC/ISH aspects ranging from CHL to DLBCL/PMBCL in the same tumour. These features were consistent with BCLU-DLBCL/CHL.

PMBCL and classical Hodgkin lymphoma of nodular sclerosing subtype (CHL-NS) present as an anterior mediastinal mass with involvement of the thymus and/or supraclavicular lymph nodes. BCLU-DLBCL/CHL usually presents with mediastinal manifestations, but also includes occasional cases involving non-mediastinal lymph node sites and rarely primary extranodal involvement. In contrast to PMBCL, non-lymphoid organs are rarely infiltrated and involvement of lung (by direct extension), liver, spleen, and bone marrow are documented. [1]. In our report, case 2 was diagnosed from bone marrow and CT scan demonstrated left axillary lymphadenopathy and left mammary tumour but did not reveal any mediastinal tumor.

PMBCL and CHL-NS preferentially affect young women, but BCLU-DLBCL/CHL is more common in young men with ages between 20 and 40 years. However, they have been reported in individuals as young as 13 years of age, and in older adults beyond the age of 70 [1]. Eberle et al. [3] reported 33 cases of gray-zone lymphoma, of which 27% had no mediastinal involvement. Interestingly, those without mediastinal disease were significantly older (median age 55). In our report, one case is 11 years old and another one is 65 years old. The other two cases are between 20 and 40 years. Additionally, only one case is a woman and her age is 27.

According to previous reports [3,5,6], DLBCLU-DLBCL/CHL shares histopathological features of CHL and DLBCL. From the morphological point of view, BCLU-DLBCL/CHL shows typically sheet-like, confluent growth of pleomorphic tumour cells embedded in a diffusely fibrotic stroma. There is
variability from area to area. The majority of tumour cells classically resemble lacunar cells and Hodgkin cells. However, the tumour shows marked variation of morphological aspects ranging from CHL to DLBCL/PMBCL in the same tumour. There is usually a sparse inflammatory infiltrate present with only scattered eosinophils, lymphocytes, and histiocytes. Typically necrotic areas do not include neutrophilic infiltrates [7]. In our report, case 1 resembled CHL-NS. All of the cases showed variable sheet-like, confluent growth of pleomorphic tumour cells with many surrounding reactive lymphocytes and histiocytes, fewer eosinophils and neutrophils and sparse plasma cells.

BCLu-DLBCL/CHL presents with overlapping clinical, morphological, and IHC features of CHL and DLBCL, particularly nodular sclerosis CHL and PMBCL. Immunohistochemically, an intermediate character between CHL and DLBCL is also seen in BCLu-DLBCL/CHL. There are transitional features between DLBCL/PMBCL and CHL. Diagnostic criteria include, for example, cases morphologically resembling PMBCL but with strong expression of CD15, absence of CD20 or presence of EBV [1]. Cases rich in tumour cells resembling CHL, which are strongly positive for CD20 and/or other B-cell markers, are also included in this category [7]. B-cell program is usually preserved in the tumour cells with expression of the transcription factors PAX5, OCT 2, BOB.1, and CD23 but this profile is accompanied by expression of typical “CHL markers” like CD15 and CD30 [6]. The most common immunophenotype included the expression of CD20, CD30 and CD45, in addition to which CD15 and EBV are expressed in a subset of cases. Gualco G, et al. (6) reported that CD20 and CD30 were the two most frequent markers expressed and were present in all cases in their series. The cases also showed a high frequency of expression of CD79a (8/8) and PAX5 (10/10) even in Reed–Sternberg-like cells. CD45 was absent in only 1 case [6]. All of our 4 cases included CD20, PAX5 and CD30 positivity, but CD79a was negative in three cases and variable in one case. The cases also showed a low frequency of expression of CD45 (1/4). CD15 and CD23 were negative in all of the cases.

The existence of B-cell lymphoma, unclassifiable, with features intermediate between primary mediastinal B-cell lymphoma and classical Hodgkin lymphoma with EBV expression is described in the WHO 2008 classification. The frequency of EBV in this borderline category is yet to be determined as only a few cases have been reported in the literature. In the Traverse-Glehen et al. [2] series, 2 of 7 cases showed evidence of EBV, while Minami et al. [8] and Quintanilla-Martinez et al. [9] reported one case each. In the Gualco G, et al. [6] series, 2 of 10 cases were associated with EBV. In the present study, 2 of 4 cases showed evidence of EBV. Either immunohistochemistry for EBV (LMP1) or ISH for EBER were positive in one case, but only ISH for EBER was focally positive in patchy areas of the other case.

In this study, we presented 4 occasional non-mediastinal BCLu-DLBCL/CHL cases and discussed them in the light of literature.

FIGURES
Figure 1: a. Excisional biopsies of a left axillary lymph nodes exhibit a nodular growth pattern with fibrous bands and many Reed–Sternberg (HRS) -like cells and lacunar cells (H&E, x200).

Figure 1: b. The large atypical cells strongly express CD20 (Immunoperoxidase stain, x200).
Figure 1: c. The large atypical cells are negative for CD79a (Immunoperoxidase stain, x200).

Figure 2: a. The trephine biopsy of bone marrow shows the proliferation contained many histiocytes, fewer small lymphocytes and rare plasma cells, eosinophils and neutrophils with many large atypical cells consistent with HRS cells and some variants in diffusely fibrous stroma (H&E, x200)
Figure 2: b. The large atypical cells strongly express CD20 (Immunoperoxidase stain, x200).

Figure 2: c. The large atypical cells are negative for CD79a (Immunoperoxidase stain, x200).
Figure 3: a. Excisional biopsies of a left axillary lymph nodes showed many Hodgkin’s and HRS cells with surrounding many reactive lymphocytes and histiocytes but some plasma cells, eosinophils and neutrophils (H&E, x200).

Figure 3: b. The large atypical cells strongly express CD20 (Immunoperoxidase stain, x200).
Figure 3: c. The large atypical cells are negative for CD79a (Immunoperoxidase stain, x200).

Figure 4: a. Excisional biopsy of the inguinal lymphadenopathies shows sheet-like, confluent growth of pleomorphic tumour cells with surrounding many reactive lymphocytes and histiocytes, fewer eosinophils and neutrophils and rare plasma cells (H&E, x200).
Figure 4: b. The large atypical cells strongly express for CD20 (Immunoperoxidase stain, x200).

Figure 4: c. The large atypical cells are variably positive for CD79a (Immunoperoxidase stain, x200).
REFERENCES