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Cytological-Pathologic Correlation

The utility of CD83, fascin and CD23 in the differential diagnosis of primary mediastinal large B-cell lymphoma versus classic Hodgkin lymphoma☆

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ABSTRACT

Primary mediastinal large B-cell lymphoma (PMBL) and classic Hodgkin lymphoma (CHL) are the most common large cell lymphomas arising in the mediastinum and are thought to be closely related histogenetically. Although the distinction between PMBL and CHL is usually straightforward, in some cases it is challenging and rarely these neoplasms have intermediate features and qualify for the diagnosis of mediastinal gray zone lymphoma (GZL). CD83 and fascin are markers of CHL and CD23 is a marker of PMBL. In this study we assess the utility of this combination of these immunohistochemical markers to distinguish CHL from PMBL. We retrospectively collected cases of PMBL, CHL and GZL from three centers. Tissue sections were stained with CD83, fascin and CD23. CD83 was expressed in the neoplastic cells of 100% of CHL (22/22), 93% of GZL (16/18) and 41% of PMBL (9/22). Similarly, fascin was positive in the neoplastic cells of 100% of CHL (22/22), 86% of GZL (18/21) and 32% of PMBL (7/22). CD23 was positive in 95% of PMBL (21/22), 67% of GZL (12/18) and 9% of CHL (2/22). CD83 and fascin are sensitive markers for CHL but not specific whereas CD23 is sensitive for PMBL and uncommon in CHL. The GZL cases in this study had an intermediate immunophenotype, but the results were closer to CHL than PMBL. A large panel of immunohistochemical studies is recommended to distinguish CHL from PMBL entities and we suggest that CD83, fascin and CD23 add value to panels designed for this differential diagnosis.

1. Introduction

Primary mediastinal (thymic) large B-cell lymphoma (PMBL) is a distinctive type of diffuse large B-cell lymphoma (DLBCL) involving the mediastinum and is thought to arise from thymic B-cells. This neoplasm usually presents as an anterior mediastinal mass and patients may have symptoms related to local invasion and compression. The neoplastic cells are medium to large in size, surrounded by compartmentalizing fibrosis, and express B-cell markers as well as CD30 heterogeneously and usually lack surface immunoglobulin. Classic Hodgkin lymphoma (CHL) is the main differential diagnosis as these neoplasms can arise in the mediastinum and mimic PMBL clinically and microscopically [1]. In some patients, a mediastinal neoplasm may have morphologic and immunophenotypic features significantly overlap between these two diseases, and these neoplasms have been designated B-cell lymphoma, unclassifiable, with features intermediate between classic Hodgkin lymphoma and diffuse large B-cell lymphoma, also known as gray zone lymphoma (GZL) [2].

The distinction between PMBL and CHL is essential as the treatment of patients with these neoplasms is substantially different, despite the challenges in their differential diagnosis [3]. There have been many studies in the literature exploring various immunohistochemical panels that can be useful in establishing the correct diagnosis. CD83, fascin, and CD23 have been reported in earlier reports. In this study, we investigate the utility of combining CD83, fascin and CD23 to distinguish PMBL from CHL. We also assess this combination in a group of cases of GZL.

2. Material and methods

2.1. Samples

Cases of PMBL, mediastinal CHL and GZL were retrospectively retrieved The diagnoses of these entities were established according to criteria described in the WHO classification [2]. Formalin-fixed, paraffin-embedded tissue blocks were retrieved and unstained slides were

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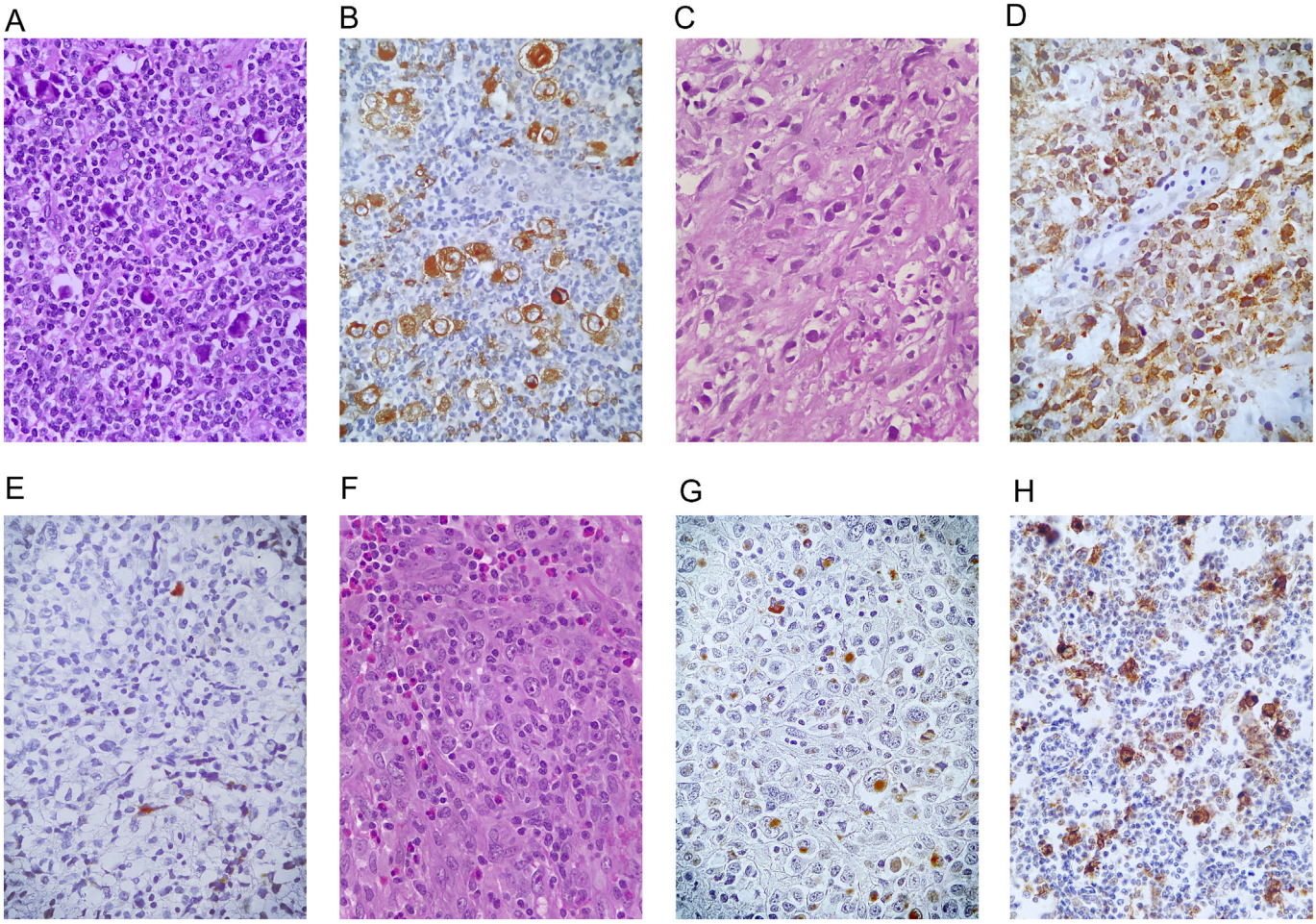

Fig. 1. A case of CHL showing numerous Reed-Sternberg and mononuclear Hodgkin cells that are positive for CD30, CD15 and negative for B-cell markers (A), and is strongly positive for CD83 in membranous and cytoplasmic pattern, with Golgi area accentuation (B). Hematoxylin and Eosin image of a case of PMBCL (C), which shows a diffuse positive for CD83 (D). Another case of PMBCL that is negative (E) for CD83, note the positive dendritic cells in the background. A case of GZL where neoplastic cells resemble Hodgkin cells and are positive for CD30, CD15, CD45 with preservation of B-cells markers (F), and is positive for CD83 in Golgi pattern (F). Another GZL case that shows diffuse positivity for CD83 (G).

cut. The study was approved by the Institutional Review Board.

2.2. Immunohistochemistry

We used 4-μm thick formalin-fixed, paraffin-embedded tissue sections, heat-induced epitope retrieval, and an avidin-biotin complex detection method. Staining was performed in an automated immunostainer (Ventana Medical Systems). Antibodies, dilutions and sources were as follows: CD83 (1:20, Leica Biosystems, UK), fascin (ready to use, Cell Marque Corporation, USA, and CD23 (ready to use, Biogenex, Netherlands). An external positive control was performed in each batch. In addition, internal control cells were evaluated with appropriate results in each case. To assess the reproducibility of immunohistochemical data, interpretation was performed by two pathologists in order to confirm true neoplastic cell positivity instead of background cells. A cutoff of 10% of cells was required for each marker in order to label a case as positive. As tissue preservation was different from case to case, both bright and dim staining was considered positive.

3. Results

3.1. Immunostaining patterns

The pattern of reactivity for CD83 was similar, membranous and cytoplasmic, in positive cases. In addition, in CHL cases the HRS cells commonly showed a Golgi-like pattern of reactivity and some cases showed only cytoplasmic Golgi (dot)-like positivity. Background dendritic cells were also positive (Fig. 1A–E). The pattern of fascin reactivity was membranous and cytoplasmic in all positive cases. Background histiocytes and endothelial cells were also positive (Fig. 2A–H). In PMBL CD23 was positive in a membranous fashion, usually diffusely. In contrast, cases of CHL showed bright but focal CD23 expression in HRS cells (Fig. 3).

Interobservor agreement was good for the interpretation of all three markers. In some tumors, interpretation of fascin was more challenging than CD83 and CD23 in core needle biopsy specimens because of the presence of brisk vascularity and numerous histiocytes in the background.

3.2. Results for each lymphoma type

In PMBL, 21 of 22 (95%) cases were positive for CD23, diffusely throughout the neoplasm in 16 (76%) cases and was focal in 5 (24%) cases. CD83 was positive in 9 of 22 (41%) and fascin was positive in 7 of 22 (32%) neoplasms.

In CHL, all 22 cases assessed were positive for CD83 and fascin. CD23 was positive in 2 (9%) cases. Cases of GZL were positive for CD83 in 16 of 18 (93%), fascin in 18 of 21 (86%), and CD23 in 12 of 18 (67%).

Comparing CHL with PMBL, none of the markers individually could

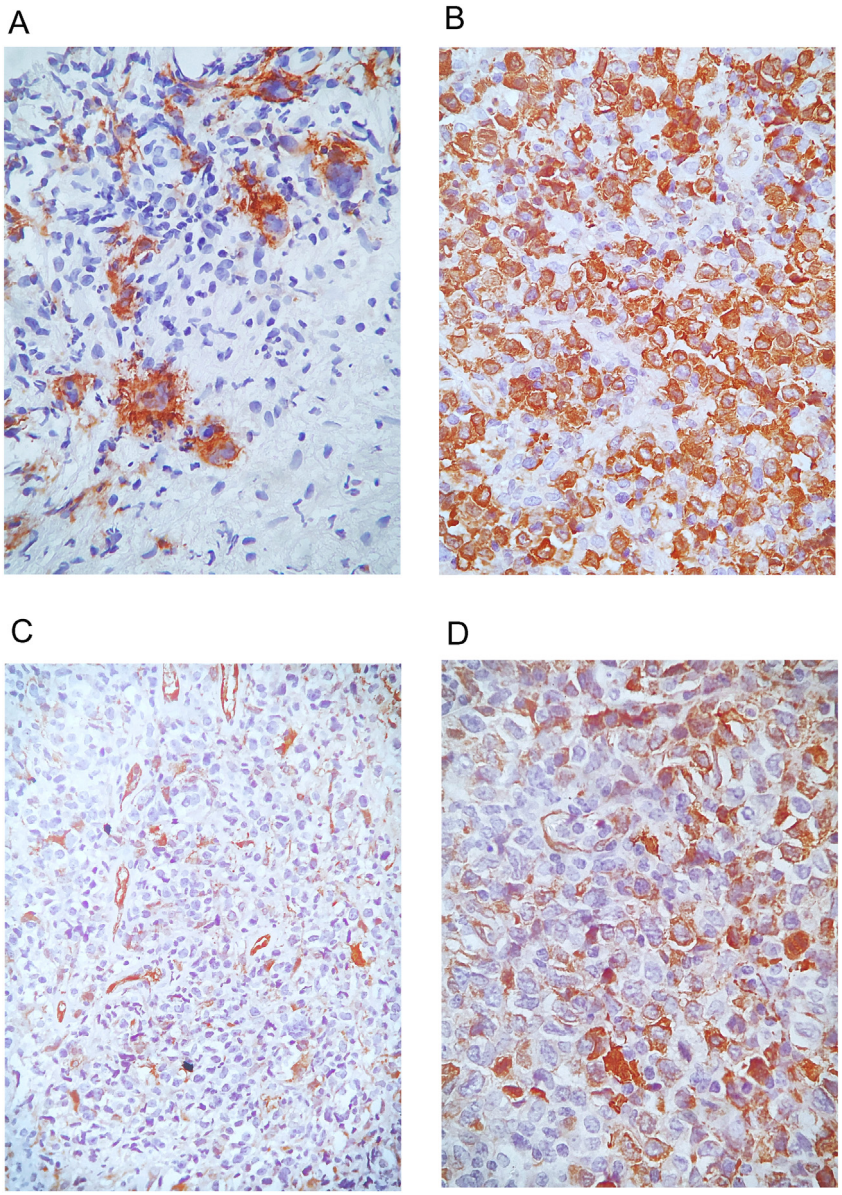

Fig. 2. Immunohistochemical staining for fascin is positive in CHL (A) and in some cases of PMBL (B). Another case of PMBL that is negative. Note the positivity in endothelial cells and scattered histiocytes (C). A case of GZL that shows a variable reactivity in the cells, a feature is also seen in CHL and PMBL (D).

perfectly discriminate between these neoplasms. CD83 and fascin provided high sensitivity and a high negative predictive value (100% each) for the diagnosis of CHL. However, the specificity for CD83 was 60% and was 69% for fascin. Similarly, the accuracy for CD83 was 80% and for fascin it was 84%. CD23 also showed a high sensitivity and negative predictive value of 95% each for PMBL, and had excellent specificity and accuracy, 91% and 93% specificity.

Combining the results of these three markers is more powerful. The combination (CD83+, fascin+, and CD23−) was 100% specific for CHL in this study. Conversely, the combination of (CD83−, fascin−, and CD23+) was 100% specific for PMBL.

4. Discussion

Distinguishing PMBL from CHL can be difficult in some patients as these neoplasms can show overlapping morphologic and/or immunophenotypic features. Nevertheless, distinguishing these diseases is essential because the therapies and prognosis for patients with these neoplasms differ [3]. Immunohistochemical studies are essential for this differential diagnosis and various antibodies have been used although there is no consensus antibody panel. In this study, we explored the utility of CD83, fascin, and CD23 in the differential diagnosis of PMBL versus CHL. We also assessed cases of GZL to determine if these markers have value for this diagnosis.

CD83 is a membrane glycoprotein belonging to the immunoglobulin superfamily that has been widely used as a surface marker of mature dendritic cells in a sustainable pattern, in contrast with transient expression in activated macrophages and monocytes [4]. CD83 is also expressed in non-proliferating subset of germinal center B-cells [5] and is believed to have a regulatory role on T and B-lymphocyte maturation, culminating in immune suppression [5,6]. The utility of CD83 in histopathology practice dates back to 1997, when Sorg et al. reported a high frequency of expression pattern by Hodgkin cells [7], confirmed in additional studies [8,9].

To the best of our knowledge, this is the first study to investigate the potential value of CD83 in the differential diagnosis of mediastinal lymphomas. According to our results, the high expression of CD83 in CHL and moderate expression in PMBL has diagnostic utility, especially

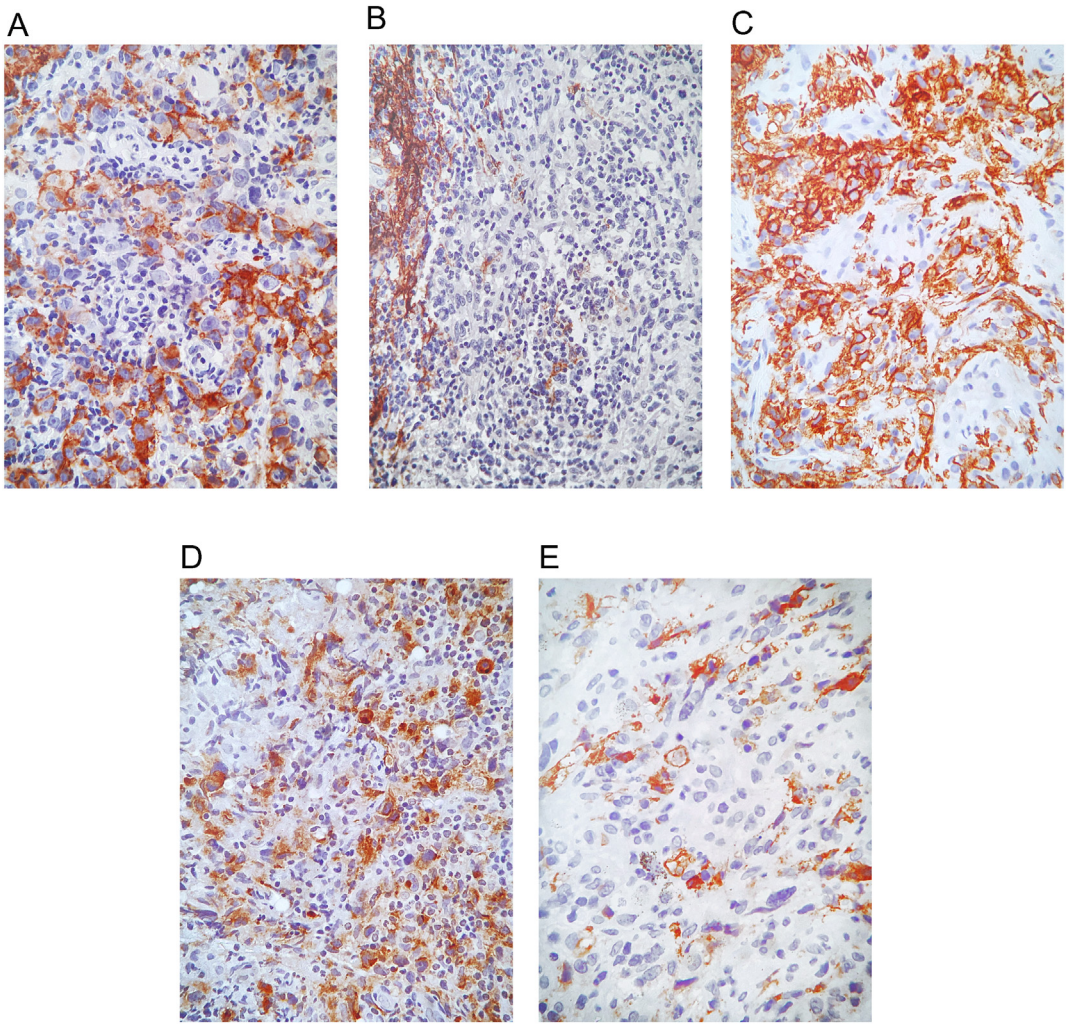

Fig. 3. CD23 immunohistochemical stain: a rare case of CHL that is positive in a subset of HRS cells (A). Most cases of CHL are negative, the positivity is limited to germinal centers, while HRS are negative (B). The majority of PMBL are positive for CD23 (C). In GZL, the results are variable. This case is positive (D), while in this case, large cells are negative and the stain shows non-specific positivity in few background small cells (E).

Table 1
Results of immunohistochemical staining for CD83, fascin and CD23 among CHL, GZL and PMBL cases. CD83 and fascin were sensitive in CHL, while CD23 in PMBL. GZL cases showed intermediate results. CHL: classic Hodgkin lymphoma, GZL: gray zone lymphoma, PMBL: primary mediastinal large B-cell lymphoma.

	CHL	GZL	PMBL
CD83	100% (22/22)	93% (16/18)	41% (9/22)
Fascin	100% (22/22)	86% (18/21)	32% (7/22)
CD23	9% (2/22)	67% (12/18)	95% (21/22)

when the result is negative in a suspected case of PMBL. Moreover, 3C12C-MMAE is a human anti-human anti-CD83 antibody that was tested as a targeted therapy and eliminated CD83-positive HRS cells [9]. Thus, the results of this study shed light on a potential therapeutic target for PMBL and GZL.

Fascin is an intermediate filament-protein that is important for actin-cross linking. It is normally present in cells with extensive surfaces or migratory potential, such as neurons, dendritic cells, macrophages and endothelial cells [10]. Whereas normal lymphoid cells are uniformly non-reactive, fascin expression has been observed in Hodgkin Reed-Sternberg cells (HRS) in most cases of CHL [11], as well as in ALCL and a subset of cases of DLBCL [12,13]. Our results are in agreement with earlier reports. All cases of CHL in this study had fascin-positive HRS cells. In mediastinal lymphomas, one recent study reported that 53% of PMBL are positive for fascin, relatively close to the 32% frequency in PMBL observed in this study [14].

CD23 is a low affinity receptor for IgE that is important for regulation of its own expression level. CD23 also functions as a lymphocyte growth factor on mature follicular B-cells, activated macrophages, eosinophils, and follicular dendritic cells. Expression of CD23 in PMBL is well documented in the literature, with a frequency ranging from 70 to 85%, slightly lower than the 95% frequency observed in PMBL in this study [15,16]. CD23 has been less rigorously assessed in CHL. In two studies, CD23 was positive in HRS cells of 1.3% and 10% of CHL cases, respectively [16,17], consistent with the results of this study.

Mediastinal GZL is a rare B-cell neoplasm that exhibits clinical, histologic and immunophenotypic features intermediate between PMBL and CHL. Currently; there are no consensus diagnostic criteria available by which these tumors can be classified. Lineage plasticity in neoplastic thymic precursor B-cells is one possible explanation for the emergence of GZL. The diagnosis of GZL usually requires an extensive panel of immunohistochemical markers for diagnosis. Overall, the neoplastic cells of GZL express CD30, CD45, CD20, CD79a, OCT2, BOB1, and strong PAX5. CD15 is expressed in 50–80% of cases with DLBCL morphology. GZL is an aggressive tumor and patients do not respond well to therapeutic regimens of CHL. Thus, distinguishing GZL from CHL and

PMBL is clinically relevant [2,3]. The results in this study show that GZL are usually positive for CD83 and fascin and two thirds of cases are positive for CD23. Therefore, in accord with the literature the cases of GZL in this study had an intermediate immunophenotypic profile, but closer to CHL than to PMBL.

In summary, we evaluated the utility of CD83, fascin and CD23 in the differential diagnosis of CHL and PMBL (Table 1). Although no single marker was completely sensitive and specific, this three-antibody panel is useful in reaching a correct diagnosis. CHL showed uniform expression for both CD83 and fascin, whereas PMBL was positive in less than half of cases. In contrast, CD23 expression supported the diagnosis of PMBL, especially when either CD83 or fascin was negative. Although GZL was markedly heterogenous with no specific pattern, the overall results seem to be closer to CHL than PMBL. We suggest that CD83, fascin and CD23, in addition to commonly used markers, are useful for the differential diagnosis of CHL and PMBL.

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