CORRESPONDENCE

Diagnostic Dilemmas in Aggressive Large B Cell Neoplasms with Enigmatic Immunohistochemical Profile: How Far Should We Investigate?

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Dear Editor,

Aggressive large B-cell neoplasms include many disparate entities with marked differences in morphology, phenotype, molecular pathogenesis and clinical behavior, which affect the prognosis and require tailored therapy [1]. Differential diagnosis of plasmablastic lymphomas, from plasma cell myeloma with plasmablastic morphology, as well as Diffuse Large B-Cell Lymphoma (DLBCL) with secretory differentiation is still a common problem due to a lack of a distinctive phenotype [2]. Here, we report a case where multiple diagnostic modalities were applied in tandem to reach a conclusive diagnosis but still a consensus was difficult to achieve.

A 46-year-old female presented with complaints of left-sided chest pain, radiating to the left subscapular region for one week and dyspnea for last 1–2 months. Physical examination was unremarkable. Complete hemogram showed HB = 97 g/L, TLC = 6.9×10^9 /L with a differential count of N:40 L:46 M:011 Blast:01 My:01 PC:01; nRBC:4/100 WBCs and Platelet count = 83×10^9 /L. Peripheral smear showed rouleaux formation with thrombocytopenia and occasional plasmacytoid cells. Serum calcium levels and renal function tests were within normal limits. Viral serology was negative. Skeletal survey

showed no lytic/sclerotic lesions. Chest CT showed multiple nodules in bilateral lung upper lobes, paravertebral soft tissue masses, largest being at D4 para-vertebral region measuring 3.1 cm × 2.6 cm and extending into left neural foramina, along with mild left pleural effusion. Magnetic Resonance Imaging of whole spine showed multiple para-vertebral soft tissue lesions with focal bony involvement and neural foramina compromise. A working clinico-radiological diagnosis of multiple myeloma was made and further work-up was advised. Serum LDH was 1158 U/L. Serum beta2-microglobulin level was markedly raised (1541.6 nmol/L). Serum protein electrophoresis showed a distinct M-band in the gamma region (15 g/L), which was found to be of IgA/kappa subtype on serum immunofixation studies. Bone marrow aspiration smears revealed near-total replacement of normal hematopoietic components by large atypical cells (65%) having high N/C ratio, prominent nucleoli and moderate amount of deeply basophilic cytoplasm with some of them showing eccentric nuclei. Bone marrow biopsy as well as the CT guided biopsy from D4 left para-vertebral soft tissue mass showed similar features comprising of diffuse proliferation of large neoplastic cells with central to eccentric, large hyperchromatic nuclei, few of them showing prominent nucleoli with brisk mitosis (Fig. 1). No intra-cytoplasmic or intra-nuclear inclusions were noted. Overall features were suggestive of a high grade Non Hodgkin Lymphoma (NHL) with plasmablastic differentiation and differential diagnosis included plasmablastic lymphoma, plasmablastic myeloma and DLBCLs with marked secretory differentiation. On IHC using primary backbone markers, these large neoplastic cells were strongly and diffusely positive for CD20, CD138, CD79A, bcl-2 and LCA with clonal restriction for kappa light chain (ISH) (Fig. 1). EBER expression (by ISH) was negative. In view of diffuse bone

Disclaimers: The identity of the patient is not disclosed here in this case.

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Fig. 1 **a** Bone marrow aspirate smears showing large atypical cells with plasmablastic/plasmacytic features. **b, c** Bone marrow biopsy and paravertebral soft tissue mass showing diffuse infiltration with

large neoplastic cells, with eccentric large, hyperchromatic nucleus, few of them showing prominent nucleoli with brisk mitosis. **d** LCA, **e** CD20, **f** CD79a, **g** CD138, **h** Ki-67 and **i** Kappa light chain

marrow involvement along with strong LCA and CD20 positivity and negative expression of EBER in this immunocompetent patient, possibility of plasmablastic lymphoma was largely ruled out. The secondary panel of antibodies was applied for further subtyping on which CD10, PAX-5, Cyclin-D1, CD56, CD30, ALK-1, bcl-6 and MUM1 were found to be negative and MIB-1 index was ~90%. Meanwhile, Interphase FISH studies for myeloma panel revealed t(14;16) translocation in 08% cells. In view of the findings mentioned above, the differentials were overlapping between plasma cell myeloma with plasmablastic differentiation and conventional DLBCLs with plasmacytic/plasmablastic morphology and marked secretory differentiation. However, strong and diffuse CD20 and LCA positivity along with negative MUM1 expression prompted us to favor a final diagnosis of DLBCL with plasmacytic/plasmablastic morphology and marked secretory differentiation.

This case is one example where aggressive large B-cell lymphomas with plasmablastic/plasmacytic differentiation show overlapping features with plasmablastic myelomas due to a lack of distinctive phenotype as they are thought to be derived from terminally differentiated B cells, exhibiting an immunophenotype of plasma cells [2]. Findings in favor of plasmablastic myeloma include monoclonal gammopathy of IgA/kappa type, IHC showing CD138+ (diffuse and strong) immunophenotype, negativity for PAX-5 and presence of a rarer translocation t(14;16) which is known to be significantly associated with positive expression of CD20 and worst overall prognosis according to a recently published study [3]. Also, infrequently though, plasma cell myeloma with mature small cell morphology and presence of t(11;14) have been found to express CD20 in few patients and may represent their cellular origin from the immature plasma cell stage close to the lymphoplasmacytes [4].

The points favoring the possibility of DLBCL—non-Germinal Centre B (GCB) type with secretory differentiation include absence of lytic bone lesions, diffuse bone marrow involvement (reported in as many as 10–25% of DLBCL cases) [1], detection of surface and/or cytoplasmic immunoglobulins (IgG > IgM > IgA type) (described in 50–75% of the cases) [5] and immunophenotype showing diffuse and strong positivity for CD20 and LCA with negative expression of MUM1. Moreover, t(14;16) translocation is neither a frequent finding in myeloma patients (with a reported overall incidence of 3%) [6] nor is it specific for multiple myeloma, and it has been reported in IRF8-associated DLBCLs as well as CBFA2T3/ACSF3 locus associated B-cell lymphomas [7, 8]. Also, the study by Narita et al. [3] does not throw light on the intensity of expression of CD20 and CD45 as well as the morphology of plasma cells (whether blastic or mature plasma cells) in t(14;16) associated patients. In this presented case, PAX-5 negativity was an unusual finding. Such cases may require evaluation by additional antibodies such as PRDM1/BLIMP1, the expression of which has been described in as many as 31.7% of non-GCB group DLBCLs [9]. Loss of PAX-5 expression was previously addressed by Moreno et al. [2] who documented a category of DLBCLs with BLIMP1 expression which is a marker of antibody-secreting cell differentiation and a functional repressor of bcl-6 and PAX-5.

This case is challenging as its diagnosis depends upon a combination of investigations but some questions still remain unanswered, thus emphasizing on the need for more evidence-based diagnostic modalities to segregate the overlapping differentials. A definitive conclusion would require complementation with novel molecular methods such as gene expression profiling and next-generation sequencing. Moreover, a clinician's approach would be more individualistic as these patients may respond poorly to conventional therapies such as rituximab and bortezomib and may require targeted therapies to optimize the treatment options.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval This case report does not contain any studies with human participants or animals performed by any of the authors.

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