CD38—Negative Myeloma with Anaplastic Morphology at Presentation: A Case Report

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Dear Editor,

CD38 is a 46-kDa type II trans-membrane glycoprotein involved in receptor-mediated cell adhesion, signal transduction and intracellular calcium metabolism. Normal plasma cells show higher expression of CD38 than the hematopoietic stem cells, T and B lymphocytes. However, malignant plasma cells over-express CD38 at all stages of maturation. In fact, high and consistent expression of CD38 by myeloma cells together with its significance in cell signaling pathways have suggested the role of CD38 as a potential target for the treatment of multiple myeloma (MM). Daratumumab is a humanized CD38 monoclonal antibody that has emerged as a breakthrough targeted therapy in myeloma patients, used both as a monotherapy and in combination with other agents. Recently published studies have documented loss of CD38 in relapsed or refractory myeloma [1]. Here, we report a case of newly diagnosed MM with CD38 negative plasma cells and anaplastic morphology as evaluated by immunohistochemistry that posed a diagnostic challenge due to such rare association.

A 32-year old male presented with complaints of dyspnea for last 1–2 months. Physical examination was unremarkable. Complete hemogram showed HB = 7.9 g/dl, TLC = $14.76 \times 10^9/L$ with a differential count of N:44 L:30 M:15 Atypical cells? Blasts:07 My:03 E:01; nRBC:7/100 WBCs and platelet count = $11 \times 10^9/L$. Peripheral

smear showed leuco-erythroblastic picture with thrombocytopenia and 07% large atypical cells. A provisional diagnosis of acute leukemia/lymphoma was made and further investigations advised. Serum albumin was 3.9 g/dl and serum LDH was markedly elevated (2444 IU/ml). 24 h urinary protein was 4.38 gm/24 h. Serum creatinine (4.8 mg/dl) and serum calcium (13.68 mg/dl) levels were raised. Viral serology for HIV, Hepatitis Band C was negative. Serum total protein was 6.1 g/dl with A:G ratio of 1.7:1 (Albumin: 3.9 g/dl; Globulin: 2.2 g/dl). MRI showed multiple partial vertebral collapses with biconcave wedged appearance of most of mid/lower dorsal vertebral segment with bulging posterior vertebral outline from D9 to L2 vertebral segments, suggestive of marrow infiltrative disorder. PET-Scan revealed metabolically active extensive bony lesions with pancreatic involvement and mild hepatosplenomegaly. Bone marrow imprint smears showed 57% large atypical cells with marked nuclear convolutions which were negative for myeloperoxidase stain. Flowcytometry could not be performed due to dry tap. Hypercellular bone marrow biopsy sections showed near-total replacement of normal hematopoietic components with undifferentiated large atypical cells with pleomorphic nuclei, conspicuous nucleoli and moderate amount of cytoplasm. The first line of immunohistochemical markers comprising of cytokeratin, desmin, S100 and LCA was negative. A possibility of LCA negative hematopoietic neoplasm was strongly considered and expanded panel of IHC markers was applied. However, CD34/CD117/TDT/CD3/MPO/CD79a/PAX5/CD4/CD61/CD20/CD30/CD38 were found to be negative. Before labeling the case as Undifferentiated /poorly differentiated malignancy, a review of the case was done. Positive clinical findings included bicytopenia, renal insufficiency, hypercalcemia and raised LDH. No M band was found on serum protein

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electrophoresis. However, serum free light chain (kappa/lambda) ratio was 0.2. In order to rule out the distant possibility of CD38 negative plasma cell neoplasm, CD138 and CD56 were applied, which came out to be positive along with clonal restriction for lambda light chain. Cytogenetics revealed normal karyotype. Serum β 2-microglobulin was raised (6.5 mg/L). Composite consideration of clinical (CRAB features+) and histomorphological findings (replacement of BM with large pleomorphic plasma cells) along with the characteristic immunophenotype (CD138++/CD56+/CD38–/CD20–/PAX5–/Cyclin D1–/CD79a–/LAMBDA++/EBER-ISH–), led to a final diagnosis of anaplastic myeloma (Fig. 1). The patient was started on Bortezomib–Dexamethasone regimen and planned for autologous stem cell transplant (SCT), once complete or very good partial response (CR/VGPR) was achieved.

There are a few interesting points about this case:

Firstly, myeloma with anaplastic morphology as seen in this case is a rare, treatment-resistant subtype more commonly observed in younger patients, associated with immunoglobulin A isotype, with predisposition for the extramedullary sites and associated with 1q21 amplification, 17p(p53) deletion, t(4;14), and/or chromosome 13 anomalies. Anaplastic morphology may present initially or as a feature of progression and is associated with an overall poor prognosis [2].

Secondly, all normal and malignant PCs express CD38 and CD138. However, the level of expression is different and allows normal PC to be distinguished from malignant PC. Expression of CD138 on myeloma cells has reportedly been variable in different studies. Witzig et al found that in multiple myeloma patient samples, up to 75% of monoclonal plasma cells did not express CD138 [3]. In contrast,

Fig. 1 **a** and **b** Peripheral smear and bone marrow aspirate smears showing large atypical cells with marked nuclear convolutions. **c** Bone marrow biopsy shows complete replacement with undifferentiated large atypical cells with pleomorphic nuclei, conspicuous nucleoli and moderate amount of cytoplasm; significant mitosis noted. **d–f** Immunohistochemistry shows positivity for CD138, CD56 and lambda light chain respectively

Matsui et al found that CD138 negative plasma cells represented only 2–5% of all abnormal plasma cells [4]. Patients with low levels of CD138 have a worse overall survival compared with high levels of CD138 in newly diagnosed as well as patients receiving high-dose chemotherapy followed by autologous SCT and respond poorly to lenalidomide [5, 6]. Presence of CD38 negative myeloma cells is a rare event observed especially in relapsed/refractory disease [1]. There is a reported incidence of only two cases out of around 1000 phenotypes of patients at diagnosis or relapse in one extensive study while in another study, all human myeloma cell lines expressed CD138 (29 out of 29) but only 25/29 expressed CD38 (4 out of 29 were CD38–) [7]. Loss of expression of target molecules on tumor cells is known to be an important resistance mechanism for antibody-based therapies but this patient had negative CD38 expression at diagnosis and so was not a candidate for Daratumumab therapy as a minimum threshold of target antigen expression is required above which complement-mediated cytotoxicity can occur. This loss may be explained by genetic or epigenetic changes within the epitope-coding regions of CD38 [1].

Thirdly, in such difficult cases, a clear distinction between plasmablastic lymphoma (PBL) and myeloma may be impossible and is clearly arbitrary in rare cases as they are morphologically and immunophenotypically identical. Features that favor PBL include association with HIV infection and EBER positivity in neoplastic cells (seen only in 60–70%). Also, bone marrow involvement has been reported at 30% in both HIV-positive and HIV-negative patients in plasmablastic lymphomas. Features favoring myeloma include the presence of monoclonal paraproteinemia, hypercalcemia, renal dysfunction, and lytic bone lesions [8].

Thus, one must always use both CD38 and CD138 in the expanded panel of antibodies while investigating a case of

seemingly undifferentiated hematolymphoid malignancy having bizarre nuclear morphology, to exclude plasma cell origin before considering the possibility of poorly differentiated neoplasm.

Compliance with Ethical Standards

Conflict of interest The authors state that there is no conflict of interest present.

Ethical Approval This case report does not contain any studies with human participants or animals performed by any of the authors. The identity of the patient is not disclosed here in this case.

Human and Animal Rights The identity of the patient is not disclosed here in this case.

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