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Letter to the editor

HLA genotype and response to nivolumab therapy in relapsed refractory primary mediastinal B-cell lymphoma

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Primary mediastinal B-cell Lymphoma (PMBCL) is an uncommon mature B-cell malignancy arising from thymic tissue and classified as a unique entity in the revised World Health Organization (WHO) for lymphoid neoplasms [1]. It presents more frequently in younger females and constitutes approximately 2–3% of all Non-Hodgkin lymphomas (NHL) [2]. PMBCL is associated with sheets of medium to large B-cells with polymorphic nuclei, with evident sclerosis and prominent collagen bands without an inflammatory background. These cells typically express B-cell markers such as CD19, 20, 23, 79a and PAX-5 while surface immunoglobulin is absent. The majority of PMBCL express CD30 but it typically weaker than that observed in other CD30 positive lymphomas. MAL protein expression is seen in about two thirds of cases which aids in differentiation from diffuse large B-cell lymphoma (DLBCL). PMBCL can also be distinguished from classical Hodgkin Lymphoma (cHL) by lack of granulocyte and lymphocyte infiltration and expression of BOB-1 and OCT-2.

Abnormalities on chromosome 9p are common in PMBCL which encode the Janus Kinase 2 (JAK2) along with programmed death ligands (PD-L) 1 and 2; this can also be appreciated on gene expression profiling. Such over-expression of PD-L has been implicated in T-cell exhaustion leading to immune evasion of the malignant B-cell [3]. Front line therapy of PMBCL includes combinational chemotherapy such as CHOP or EPOCH along with the anti-CD20 monoclonal antibody rituximab [4,5]. Positron emission tomography with computed tomography (PET/CT) can identify patients whom would benefit from consolidative radiotherapy. Relapses typically occur early after completion of front line therapy and can remain confined in the mediastinal area or spread to extra-nodal sites. In such cases, salvage chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) can result in durable remissions in patients with chemo sensitive disease [6].

Herein, we discuss a case of a 25 year old female who initially presented with a mediastinal mass causing a large pericardial effusion and internal jugular vein thrombosis. Tissue biopsy showed diffuse infiltration by large lymphoid cells with moderate cytoplasm within a sclerotic background. The neoplastic cells expressed CD 20, 23, PAX-5, MUM-1 along with CD30 in a subset of tumor cells (Fig. 1A–D). CD 3, 5, 10 and BCL6 were negative. Ki-67 was expressed at 70%. She was treated with front line CHOP-R for a total of 8 cycles with evidence of complete response. However, 4 months post completion of therapy, she presented with dyspnea and repeat imaging showed evidence of disease recurrence with PET/CT scan showing an intensely hypermetabolic mass abutting the anterior superior mediastinum and extending to the right supraclavicular region. She underwent a repeat tissue biopsy confirming disease recurrence. Subsequently, she received 3 lines of salvage chemo-immunotherapy (ESHAP-R, mini-BEAM-R and DICEP-R) but adequate chemo-sensitivity evident as partial response to permit proceeding with autologous HSCT was not achieved.

Subsequent salvage with brentuximab vedotin (Bv) as monotherapy or in combination with chemotherapy was entertained but given recent literature suggesting low response rates in this setting; this approach was abandoned [7]. In light of observed chemo-resistance, we opted for immunotherapy with a check point inhibitor using nivolumab; given as 3 mg/kg intravenously at 2 week intervals. Following the third dose, she developed zoster reactivation on the right T4 dermatome treated with valacyclovir which has subsequently recovered without neuralgia. Following 2 months of therapy, repeat PET/CT scan showed significant interval improvement of metabolic activity within the mediastinal mass with standardized uptake value (SUV) of 2.5 from 29 (liver SUV 3.9) prior to nivolumab initiation consistent with complete metabolic response (Fig. 2). She received 15 cycles of therapy to date with sustained response and without other adverse events including autoimmune toxicity. Her HLA type was performed showing HLA-A*02:01; 24:02 HLA-B*38:01; 44:02 HLA-C*05:01; 12:03 HLA-DRB1*11:04; 13:01 HLA-DQB1*03:01; 06:03 and HLA-DPB1*02:01; 04:01.

Patients with relapsed/refractory PMBCL (rrPMBCL) with chemo resistant disease have limited therapeutic options with poor prognosis. Furthermore, the rarity of this subtype of lymphoma is a hindering factor for clinical trial development. Expression of CD30 in PMBCL, albeit with lower intensity than other lymphomas presents an attractive target for using Bv, however the recent trial exploiting this strategy showed inadequate response rates [7]. Given the over-expression of PD-1 ligand and the impressive activity of anti-PD-1 antibodies in cHL, Zinzani et al., examined the role of pembrolizumab in rrPMBCL as part of the KEYNOTE-013 trial with 17 patients evaluable for response [8]. Among this cohort, 2 patients (11.8%) achieved a complete response (CR) with an overall response rate (ORR) of 41%. Another anti-PD-1 antibody, nivolumab, was granted approval by the U.S. Food and Drug Administration (FDA) for cHL failing autologous HSCT and Bv as well as in solid malignancies including metastatic

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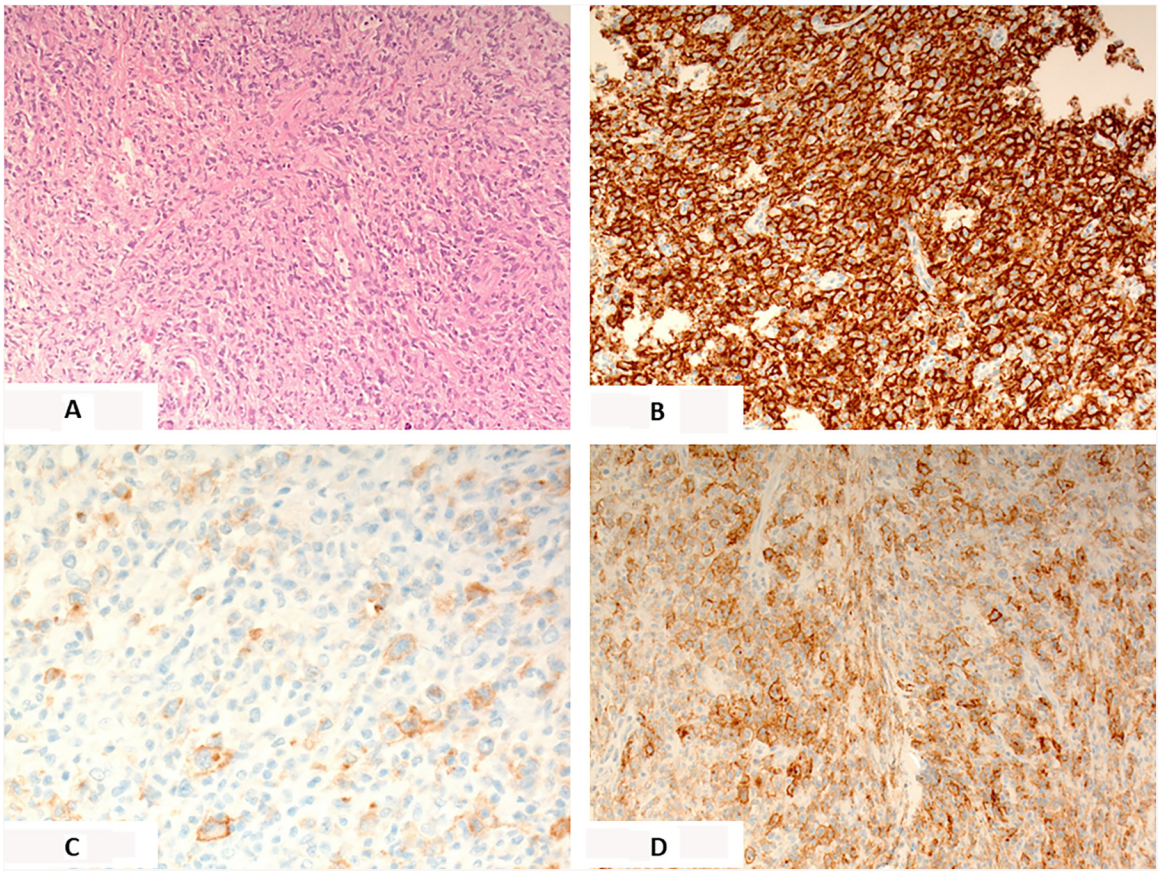

Fig. 1. (A) Diffuse infiltration by large lymphoid cells with moderate cytoplasm on sclerotic background, H&E stain, 100×. (B) The tumor cells are positive for CD20 immunostain. (C) A subset of tumor cells are positive for CD30 immunostain. (D) There is diffuse positive staining for CD23 immunostain.

melanoma, renal cell carcinoma and squamous cell lung cancer [9]. A recent case report using nivolumab in rrPMBCL yielded complete response with autoimmune toxicity manifesting by severe neutropenia [10].

Nivolumab is an IgG4 anti-PD-1 monoclonal antibody that unleashes the immune system against the tumor by blocking the interaction between PD-1 on surface of cytotoxic $CD8^+$ T-lymphocytes and its corresponding ligands. Complete responses to nivolumab are seen in a minority of patients and emergence of tumor resistance is not uncommon. This has been attributed to various factors such as the immune phenotype of the malignancy or the host gut microbiome. Recently, Chowell et al., hypothesized that the HLA genotype can alter $CD8^+$ T-cell recognition of the tumor and ultimately impact the efficacy of immunotherapy [11]. They observed that maximal HLA-class I loci heterozygosity along with HLA-B44 superfamily allele expression will improve survival in patients with metastatic solid tumors. Conversely, patients with homozygosity in at least one HLA class I locus or at HLA-DPB1 were associated with worse survival irrespective of the tumor stage or type of check point therapy used. It is speculated that patients with homozygosity will present a smaller repertoire of antigens to cytotoxic T-cells ultimately eliciting a less robust immune response. This observation was supported by evidence of higher T-cell clonality in heterozygous patients.

The significance of the case presented herein is twofold; first, it supplements the limited literature regarding the efficacy of PD-1 inhibitors for rrPMBCL and to our knowledge it is the second reported case of successful nivolumab use in this setting. Second, it was interesting to observe that our patient exhibited HLA class I and HLA-DPB1 heterozygosity as well as HLA-B44 expression, all of which were recently reported as favorable variables for outcome in patients with solid malignancies. Such early reports add further insight that HLA genotype could serve as a surrogate for outcome which would have significant implications for prospective trial design. In conclusion, the use of checkpoint inhibitors in rrPMBCL supplements the therapeutic armamentarium for these patients and further examination of HLA genotype in individual patients to optimally determine the efficacy of PD-1 inhibitors is warranted.

Author contributions

Rehab Yassin collected data and wrote the manuscript.
Ali Hajeer designed the research and wrote the manuscript.
Saeed Alshieban collected data and wrote the manuscript.
Ghulam Syed collected data and wrote the manuscript.
Bader Alahmari interpreted data and wrote the manuscript.
Ayman Alhejazi interpreted data and wrote the manuscript.
Ahmed Alaskar interpreted data and wrote the manuscript.
Mohsen Alzahrani interpreted data and wrote the manuscript.
Moussab Damlaj designed research, analyzed and interpreted data and wrote the manuscript.

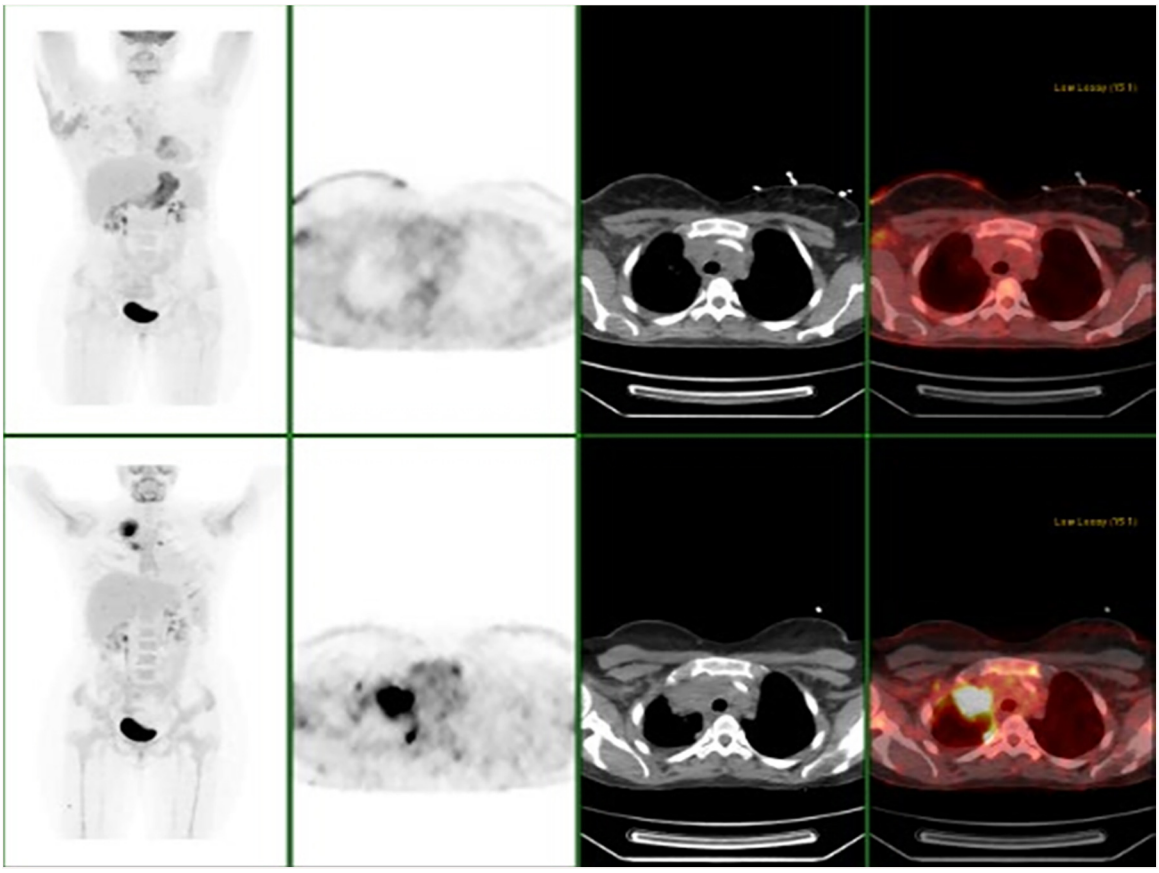

Fig. 2. Positron emission tomography/computed tomography (PET/CT) scan prior to and following nivolumab therapy in primary mediastinal B-cell lymphoma. The lower panel demonstrates the scan prior to initiation of nivolumab and the upper panel following 8 cycles of therapy demonstrating complete metabolic response.

Conflict of interest

The authors declare that they have no competing interest.

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