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CASE REPORT

Long-term complete remission in a patient with high-risk primary mediastinal B-cell lymphoma and iatrogenic symptomatic bradycardia after only two courses of DA-EPOCH-R followed by chemo-free treatment

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Abstract

Most patients with Primary Mediastinal B-Cell Lymphoma (PMBCL) are cured by rituximab and doxorubicin-based immunochemotherapy, with or without radiotherapy. In cases with relapsed and refractory (RR) disease the prognosis was historically poor. Recently, immune checkpoint-based strategies have been shown to be highly effective in patients with RR-PMBCL. We report the case of a 23-year-old woman who, due to recurring episodes of symptomatic chemotherapy-induced sinus bradycardia, was unable to receive the planned six courses of immunochemotherapy, mediastinal radiotherapy, and autologous transplantation, leading to the early initiation of a chemo-free strategy. The patient maintains a continuous complete remission at a four-year follow-up after only two cycles of immunochemotherapy followed by nivolumab plus brentuximab vedotin (BV) and pembrolizumab consolidation. Beyond describing an underreported complication of anticancer treatments, the favorable clinical outcome suggests that in PMBCL, a minimal load of chemotherapy, integrated by early PD-1 blockade, with or without BV, may be sufficient to achieve long-term disease control and cure at least in some patients.

Keywords Primary Mediastinal B-cell lymphoma · PD1-blockade · Brentuximab vedotin

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Primary mediastinal B-cell lymphoma (PMBCL) is a rare lymphoma primarily affecting young women [1]. Frontline treatment with rituximab and doxorubicin-based regimens, with or without radiotherapy, usually results in a durable complete response (CR) and cure [1, 2]. Unfortunately, 15–20% of patients experience relapse or exhibit primary refractoriness [1–3].

The prognosis for recurring patients has historically been poor, but unveiling of the genetic landscape of PMBCL has led to novel treatment options. In 60-70% of cases, tumor cells harbor structural alterations at chromosome 9p24.1, leading to overexpression of the programmed cell death ligands 1/2 (PD-L1/2) [1, 4]. This and other converging genetic mechanisms confer PMBCL, a typical immune evasion phenotype [1, 2, 5]. Consequently, PD1-blockade has emerged as a major therapeutic strategy for this malignancy [1, 5, 6]. As tumor cells express CD30, the combination with the anti-CD30 immunoconjugate Brentuximab Vedotin

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(BV) has also been explored [1, 2, 7]. Besides defining new standards for treating relapsed/refractory (RR)-PMBCL, study findings suggest that PD1-blockade, alone or combined with BV, may be highly effective in earlier treatment lines, including the frontline setting [1, 2, 5–7].

We present a PMBCL patient with chemotherapy-induced sinus bradycardia who maintained a continuous CR at a four-year follow-up after only two cycles of immunochemotherapy followed by nivolumab plus BV and pembrolizumab monotherapy.

In July 2019, a previously healthy 23-year-old woman underwent computed tomography (CT) due to worsening upper abdominal pain.

Imaging revealed a large (130×70 mm) anterior mediastinal mass with compression of the major vessels and infiltrating the parietal pleura and multiple nodular lesions involving the upper left lung lobe. An associated pleural effusion was present. Positron emission tomography (PET)-CT showed hypermetabolic uptakes in upper-anterior mediastinum (SUVmax 24.5), left supra-retroclavicular and hilar lymph nodes, and a left perigastric nodal mass (SUVmax 14.6) extending to the adrenal lodge. An ultrasound-guided core biopsy of the anterior mediastinal mass revealed involvement with medium to large-size lymphoid cells mostly arranged in cell nests compartmentalized by bands of fibrosis (Fig. 1A).

The phenotype of the lymphoid cells was assessed by immunohistochemistry, as described previously [8]. The results showed that the tumor cells expressed CD20, CD45, p63, PAX5, CD23, and BCL2. Additionally, the cells tested positive for c-Myc (30%) and were BCL6^{dim} and MUM^{dim}. They showed a strong expression of PD-L1 and displayed focal CD30 staining (Fig. 1B-E). Nanostring profiling of tumor cells with the LSTPML/Lymph2Cx (supplemental materials) was consistent with a PMBCL signature (Fig. 1F) [9]. The final diagnosis was of a stage IVA PMBCL with bulky mediastinal disease and an IPI score of 3 (stage, LDH, ECOG 2) and extrathoracic involvement [5, 10].

In September 2019, the patient, without cardiovascular comorbidities and denying use of medications or stimulants, began infusional immunochemotherapy with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R) (Fig. 2) [11].

On day 3 of the third course (October 2019), the patient experienced a sudden onset lipothymia and a significant sinus bradycardia with a heart rate of 35 beats per minute

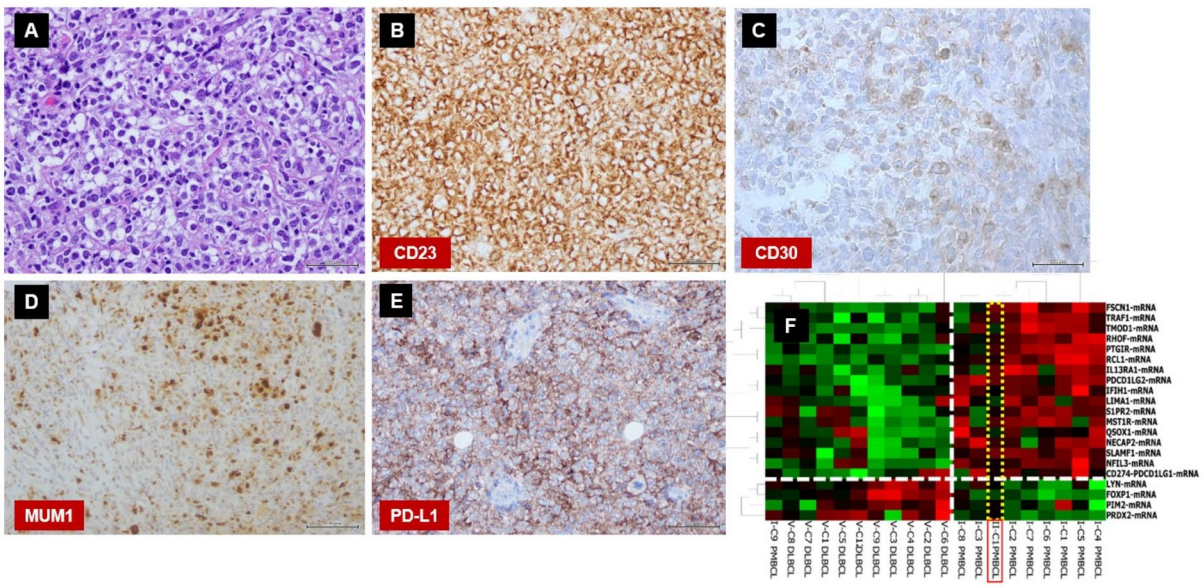

Fig. 1 Histopathologic, phenotypic and molecular features of the Primary Mediastinal B-cell Lymphoma (PMBCL) case. (**A**) Haematoxylin and eosin stain of mediastinal biopsy at diagnosis (August 2019). (**B**) CD23, (**C**) CD30, (**D**) MUM1 and (**E**) PDL-1 immunostainings. (**F**) Heatmap of gene expression in 10 cases of PMBCL and 10 cases of Diffuse Large B-Cell Lymphoma (DLBCL). Formalin-fixed, paraffin-embedded tissues from diagnostic biopsies were analyzed on a Nanostring Analyzer platform by a custom codeset of selected 63 genes (gene panel "LSTPML") based on a modification of the Lymph3Cx panel to include with additional 5 genes, differently up-regulated or down-regulated in PMBCL and DLBCL (Supplemental information). Each column represents an individual case, and results from the PMBCL patient described in the present report are encased in the red box

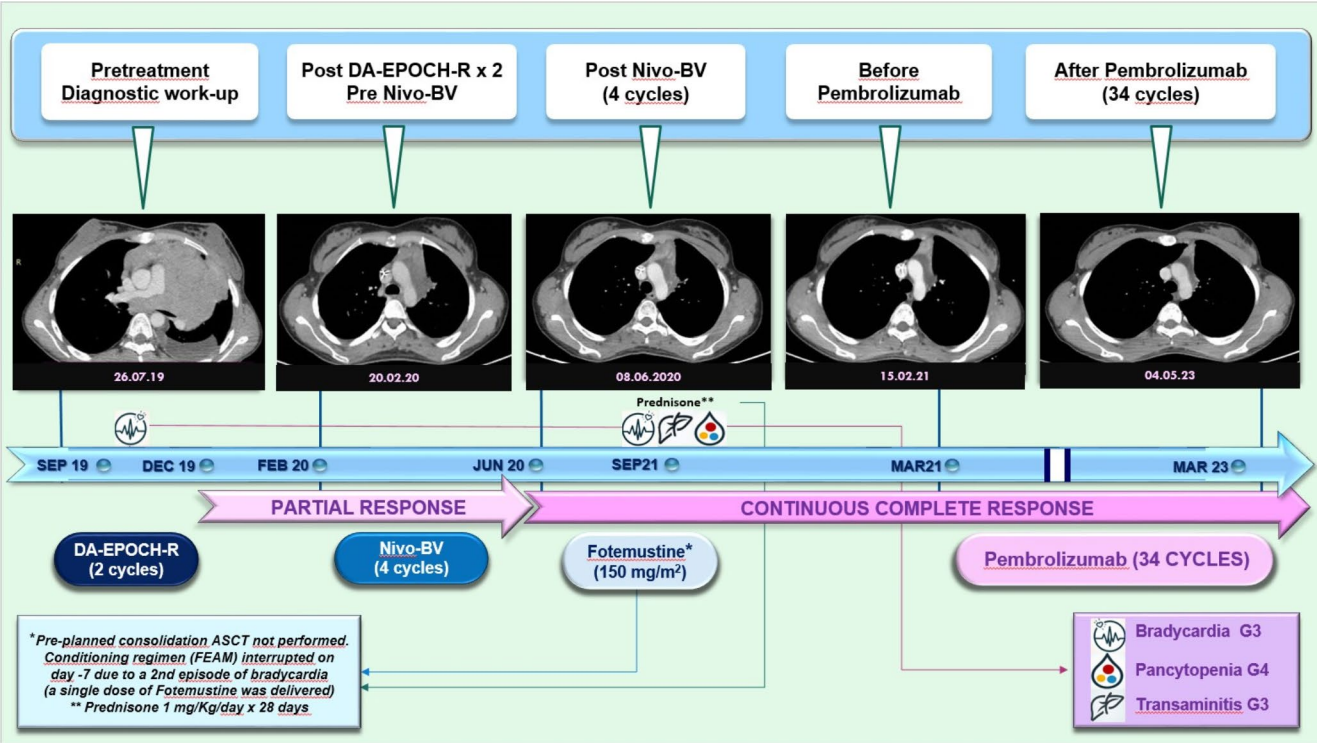

Fig. 2 Visual timeline and case summary including major clinical findings, treatments, chest computed tomography scans and toxicity episodes

(bpm) (Figure S1), which led to the discontinuation of chemotherapy. Electrolytes, renal and liver function tests were unremarkable. Holter monitoring confirmed bradycardia (43 bpm) with isolated ectopic beats and echocardiography and electrophysiological assessments were negative for congenital morpho-functional anomalies. Instrumental and laboratory assessments excluded secondary causes for bradycardia, including pulmonary embolism and thyroid dysfunction. Cardiologic consultation established a chemotherapy-induced sinus bradycardia, mandated serial electrophysiologic monitoring and, after an observation period, recommended switching to alternative treatments [12].

In February 2020, the patient was still bradycardic (47 bpm) with a mediastinal lymphadenopathy of 47 × 15 mm. She was started on a three-weekly regimen of nivolumab (240 mg/flat) and BV 1.8 mg/kg (Nivo-BV) [7]. After four courses (June 2020), a metabolic CR (Deauville score of 3) was documented with a residual mediastinal mass of 33 × 20 mm (Fig. 2).

Despite this result, we believed that our patient still required additional treatment to consolidate her response to Nivo-BV. In the original trial, 60% of patients received subsequent anticancer treatments, including autologous stem cell transplant (ASCT) and radiotherapy, after achieving a response with Nivo-BV [7]. In addition, 13 of 18 patients (70%) received subsequent anticancer therapies without previously reported progression events, evidencing a consolidation purpose [7]. Finally, our patient was considered at risk of progression due to her unfavorable profile at diagnosis (IPI score of 3, advanced stage, elevated LDH, ECOG 2, extrathoracic involvement) and the minimal load of immunochemotherapy previously received (only two courses). We attempted therefore to consolidate the response to Nivo-BV with ASCT [7].

Unfortunately, shortly after having received the first fotemustine infusion of (150 mg/m^2) of the FEAM (fotemustine, etoposide, cytarabine, melphalan) conditioning regimen, the patient developed acute pain on the right hypochondrium, radiating to the homolateral shoulder, lipothymia, and bradycardia (30 bpm) [13]. Conditioning was interrupted. Renal and hepatic function tests, electrolytes, hemodynamics, and biomarkers for cardiac damage were unremarkable, as were the thyroid and coagulation profiles. Forty-eight hours later, a stepwise increase in liver enzymes occurred, culminating in a G3 transaminitis with peak ammonia levels of 95 µmol/l, γGT of 364 U/L, and AST and ALT values of 379 U/L and 809 U/L, respectively. Laboratory indexes were unremarkable, and a viral screening (Parvovirus, Herpesviridae, Hepatitis B, and C viruses) was negative.

Treatment with acetylcysteine and methylprednisolone (1 mg/kg/die) induced a gradual improvement, and, in September 2020, she was discharged (Fig. 2). Four weeks later, the patient developed pancytopenia, requiring transfusions and growth factor support. In February 2021, the

mediastinal mass was unchanged (33 × 18 mm; SUVmax 3.6), and sinus bradycardia persisted (Fig. 2).

Due to the very limited amount of frontline immunochemotherapy received, the prolonged therapy interruptions, and the highly unfavorable features at presentation, the patient was deemed at risk of recurrence [2, 5, 10, 14]. However, cardiologists contraindicated chemotherapy and radiotherapy and, due to possible arrhythmogenic effects of antibody-drug conjugates, advised to avoid further BV [15, 16]. We opted therefore for consolidation with three-weekly single agent pembrolizumab (200 mg/flat) [6]. After 24 months of treatment (34 cycles), restaging (May 2023) confirmed a continuous CR, leading to pembrolizumab discontinuation. At 45 months from the end of the Nivo-BV regimen (March 2024), the patient remains in metabolic CR, with persistent sinus bradycardia (55 bpm) (Fig. 2).

Sinus bradycardia is an underreported complication of anticancer treatments [12, 17]. This is likely due to its low incidence and severity, as most patients are usually asymptomatic, and it is often reversible by withdrawing the offending drug [12, 17, 18]. However, it can have a proarrhythmic effect and may hinder the administration, also on a precautionary basis, of active agents with potential arrhythmogenic properties [12, 17, 18]. In our patient, two episodes of iatrogenic symptomatic bradycardia prevented the administration of the planned six courses of immunochemotherapy and mandated the early initiation of a chemo-free strategy [6, 7]. The first episode of sinus bradycardia occurred during administration of the DA-EPOCH-R regimen, and the second shortly after a single infusion of fotemustine. The bradycardia persisted but did not worsen during the administration of pembrolizumab, and no additional symptomatic episodes occurred. Interestingly, arrhythmia episodes may occur in up to 30% of patients receiving PD-1-blocking antibodies [19]. Sinus bradycardia was rarely described, with the lowest frequency reported in the case of pembrolizumab [19]. In addition, a higher reporting frequency of cardiac arrhythmias with PD1-blockers was associated with male sex and age equal to or higher than 65 years [19]. Therefore, the primary cause of bradycardia in our young female patient could likely be attributed to an alkylating agent included in DA-EPOCH-R regimen and to fotemustine [12, 17, 18].

Despite the high-risk profile at presentation our patient achieved a long-lasting CR after a minimal load of immunochemotherapy, i.e. only two courses of DA-EPOCH-R, and without mediastinal radiotherapy [1, 2, 10, 11].

In the CheckMate 436 trial, 29 RR-PMBCL patients received Nivo-BV [7]. At 3-year follow-up, median PFS was 26.0 months, while median OS was not reached [7]. However, all patients had completed an anthracycline-containing regimen; 27% had prior radiotherapy, and 13% underwent ASCT [7]. Furthermore, 60% of patients were consolidated, after Nivo-BV, with non-palliative radiotherapy, transplantation, and CAR-T cells [7]. In the Keynote 170 study of pembrolizumab monotherapy, patients with RR-PMBCL achieved 4-year PFS and OS rates of 33.0% and 45.3% [6]. Notably, at data cutoff, none of the CR patients had progressed or received subsequent treatments [6].

While these studies targeted heavily pretreated patients, the present report further highlights the potential benefit of administering chemo-free regimens earlier in the course of PMBCL. The findings suggest that a minimal load of chemotherapy along with early PD-1 blockade, with or without BV, might be enough to achieve long-term disease control and cure in some patients. It also suggests that a shorter duration of pembrolizumab consolidation could have been sufficient. Along this line, the PACIFIC study (NCT04745949) is testing a frontline lead-in treatment with Nivo-BV followed by Nivo-BV and a reduced load of doxorubicin-based immunochemotherapy.

The biology of PMBCL could help identify patients most likely benefiting from upfront chemo-free options. In about 30% of cases, the tumor microenvironment is particularly enriched for expressing immunosuppressive genes [5, 20]. These patients respond poorly to chemotherapy and may benefit from frontline PD1-blockade [20]. The present report further supports the early adoption of immune checkpoint-based strategies to counteract the immune privilege of PMBCL and minimize the load of chemotherapy necessary to achieve a cure.

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Author contributions F.V. and A.P. designed this study. C.B., A.P., A.C., L.C., and An.C. collected and integrated the clinical materials. S.C., A.D.C., S.S., D.M., and R.D.F. handled laboratory studies and analyzed results. F.V. and A.P. wrote the manuscript. All Authors critically revised the original draft and read and approved the final manuscript.

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Data availability Original data is available at https://doi.org/10.5281/zenodo.13152057 (contact the corresponding author).

Declarations

Ethics statement The study was conducted in accordance with the Declaration of Helsinki and the Institutional Review Boards-approved LYMRO-22 study (20/22 OSS; date of approval 27 July 2022, Istituto Pascale, Italy). Patients enrolled into the LYMRO-22 allow the use of

anonymized registered clinical data for scientific purposes.

Patient consent statement Informed consent has been obtained from the patient for clinical. data collection, elaboration and publication of the present report.

Conflict of interest FV declares honoraria from Hoffmann-La Roche AG irrelevant to the present research; AP declares honoraria from Hoffmann-La Roche AG, Incyte, Merck Sharp and Dohme, Bristol-Meyers Squibb and Ely-Lilly all irrelevant to the present research. AnC declares honoraria from Takeda, irrelevant to the present research. All the other authors declare no conflict of interest.

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