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LETTER TO THE EDITOR



# Pseudoprogression of triple-hit diffuse large B-cell lymphoma following polatuzumab vedotin-based salvage therapy

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Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 25% of non-Hodgkin lymphoma cases [1]. Although often treatment-responsive, 30–40% of DLBCL patients develop refractory or relapsed (R/R) disease after the current standard chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) [2]. Certain cell of origin subgroup, i.e. activated B cell type [3], or cytogenetic abnormalities, i.e. double-hit or triple-hit lymphomas [4], pose higher risk of treatment failure. Based on the recent publication from Sehn et al. [2], polatuzumab vedotin (PV) was the first antibody-drug conjugate (ADC) approved by the US Food and Drug Administration to be used in combination with bendamustine and rituximab (PVBR) in patients with R/R DLBCL who failed at least two prior therapies. By binding to CD79b on the surface of DLBCL cells, PV deploys its cytotoxic payload monomethyl auristatin E (MMAE) into the cells, which prevents microtubule formation and results in mitotic arrest and apoptosis [5]. Here we report a case of biopsy-confirmed pseudoprogression of refractory triple-hit DLBCL following PV-based salvage therapy. Our case highlights the importance of recognizing the atypical radiological response of patients with hematological malignancies treated with PV or other ADCs.

An 82-year-old female presented with new-onset small bowel obstruction due to extrinsic compression of duodenum by a large mass centered in the mesentery (Figure 1(A–C)). Biopsy and staging workup confirmed the diagnosis of Stage II DLBCL of germinal center B-cell origin (Figure 2(A–C)) with MYC (Figure 2(D)) and BCL2 (Figure 2(E)) double expressor. Fish analysis was positive for rearrangements involving MYC, BCL6 and BCL2. Her bone marrow biopsy and cerebrospinal fluid analysis were negative for evidence of lymphoma. In view of the high-risk feature of her disease, the patient was started on dose-adjusted chemoimmunotherapy with etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin in combination with rituximab (DA-EPOCH-R) with intrathecal prophylactic chemotherapy. Venetoclax was added since cycle 3 based on the results from the CAVALLI phase 1 b trial [6]. A 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography/computed tomography (18FDG-PET/CT) after cycle 3 of DA-EPOCH-R showed moderate treatment response with a small area of intense FDG uptake in the root of the mesentery with an SUVmax of 7.5 (Figure 1(D,E)). The patient tolerated the intense chemoimmunotherapy well and was able to transition from total parenteral nutrition back to oral nutrition.

An autologous stem cell transplantation (ASCT) was planned after cycle 5 of DA-EPOCH-R. Unfortunately, her pre-transplant restaging 18FDG-PET/CT revealed a minimal decrease in size, but slight increase in FDG uptake of the soft tissue in the root of the mesentery with an SUVmax of 10.5 and a few adjacent smaller mesenteric lymph nodes with intense FDG uptake, indicating treatment refractory disease (Figure 1(F,G)). Salvage chemoimmunotherapy with PVBR was commenced with the goal to achieve complete remission and attempt ASCT eventually. At the same time, potential chimeric antigen receptor (CAR) T-cells therapy was discussed with the patient and her family, but eventually declined by the patient. The patient tolerated PVBR well except for mild tumor lysis (managed as outpatient) upon treatment initiation. Response assessment 18FDG-PET/CT was performed after cycle 3, which raised a question of slightly increased prominence in intense FDG-avid portion of the mass at the root of the mesentery adjacent to the SMA takeoff (Deauville 5. The reported SUVmax was 7.5, which was slightly less than the prior exam (SUVmax 10.5). However, this was not significant when corrected for changes in background biodistribution.) (Figure 1(H,I)). The patient was however doing quite well with no new B symptoms

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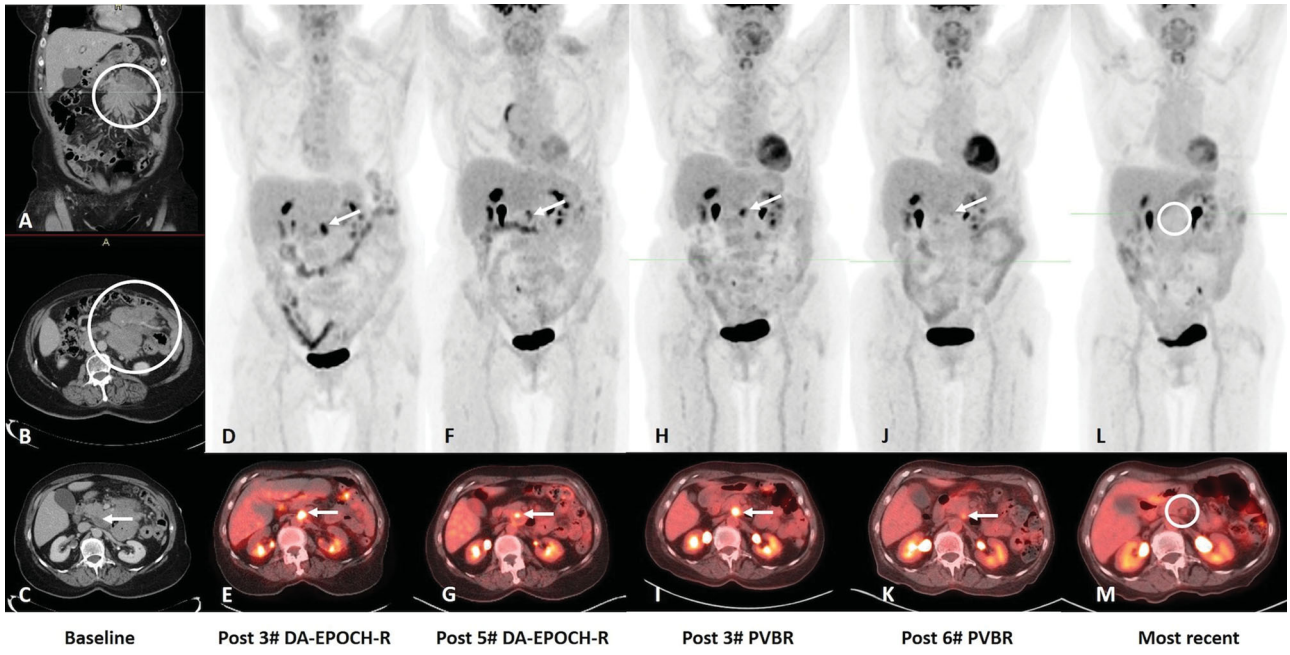


**Figure 1.** Imaging with baseline CT and serial follow up 18FDG PET/CT. (A–C) Baseline coronal and axial CT demonstrates a large mesenteric mass surrounding and encasing the vasculature (white circles) and extending up to the root of the mesentery (white arrow). (D,E) After 3 cycles DA-EPOCH-R, mid-treatment 18FDG PET/CT maximum intensity projection (MIP) and axial fusion images demonstrate a moderate initial treatment response with significant decrease in the mass size and one small area at the root of the mesentery with intense FDG uptake (white arrows) with an SUVmax = 7.5. (F,G) Follow-up 18FDG PET/CT after 5 cycles DA-EPOCH-R shows a slight decrease in size of the FDG-avid area, but slight increase in degree of uptake with an SUVmax = 10.5 (white arrows). A few additional new intensely FDG-avid mesenteric lymph nodes were seen (not pictured), indicating refractory disease. (H,I) 18FDG PET/CT after 3 cycles of PVBR demonstrates no appreciable treatment effect with a slight increase in prominence of the area near the mesenteric root, but without significant change in degree of FDG avidity (white arrows); (J,K) 18FDG PET/CT after 6 cycles of salvage chemoimmunotherapy shows significant decrease and near complete resolution of the previously seen FDG-avid area near the root of the mesentery (white arrows). (L,M) Most recent 18FDG PET/CT 6 months after treatment completion demonstrates further improvement with barely perceptible FDG uptake (white circles), consistent with Deauville 2/3.

or evidence of small bowel obstruction. Given the clinical and radiological discrepancy, an endoscopic ultrasound was performed. An adequate amount of tissue was taken from the FDG-avid mesenteric mass and an ulcerated appearing area in the duodenum, respectively. The duodenal biopsy demonstrated small bowel mucosa with mild chronic inflammation and lamina propria edema but no evidence of malignancy (Figure 2(F)). The mesenteric mass biopsy showed only sparse necrotic cells (Figure 2(G)). Therefore, PVBR was continued. A follow-up 18FDG-PET/CT after cycle 6 completion showed significant improvement in size and FDG-uptake in the FDG-avid nodular portion of the mass previously seen in the root of the mesentery (Figure 1(J,K)), which was further improved two and six months later. The most recent scan revealed near complete resolution of the previously noted FDG-avid component of the mesenteric root mass similar to slightly less FDG-avid than liver (Deauville 2/3) (Figure 1(L,M)), in keeping with at least partial, if not nearing a complete metabolic response [7]. A cyclophosphamide-based ASCT mobilization was attempted. However, the patient was unable to mount a CD34 count for feasible collection. Currently, she is managed on rituximab maintenance therapy and doing well.

The approval of PV in 2019 indicated the opening of a new era of DLBCL management, especially for patients with R/R DLBCL or patients who are ineligible for transplant and CAR T-cell therapies. ADCs have multiple advantages compared to traditional chemoimmunotherapy. Firstly, by targeting the specific subgroup of cells, ADCs significantly improve the drug delivery to the relevant cells while limiting systemic toxicity [5]. For instance, PV targets CD79-positive cells, i.e. B-cells and DLBCL cells, but spares hematopoietic stem cells [8], which makes sure that the B-cell compartment may be replenished shortly after treatment completion. Secondly, ADCs deliver its anti-cancer effect by mechanisms not only limited to the direct delivery of cytotoxic payload but also may involve the engagement of immune-mediated pathways [5]. Fuh et al. [8] reported that PV could also induce targeted cell death by antibody-mediated opsonization and antibody-dependent cellular cytotoxicity (ADCC).

Pseudoprogression has been reported in numerous solid tumors as well as hematological malignancies, such

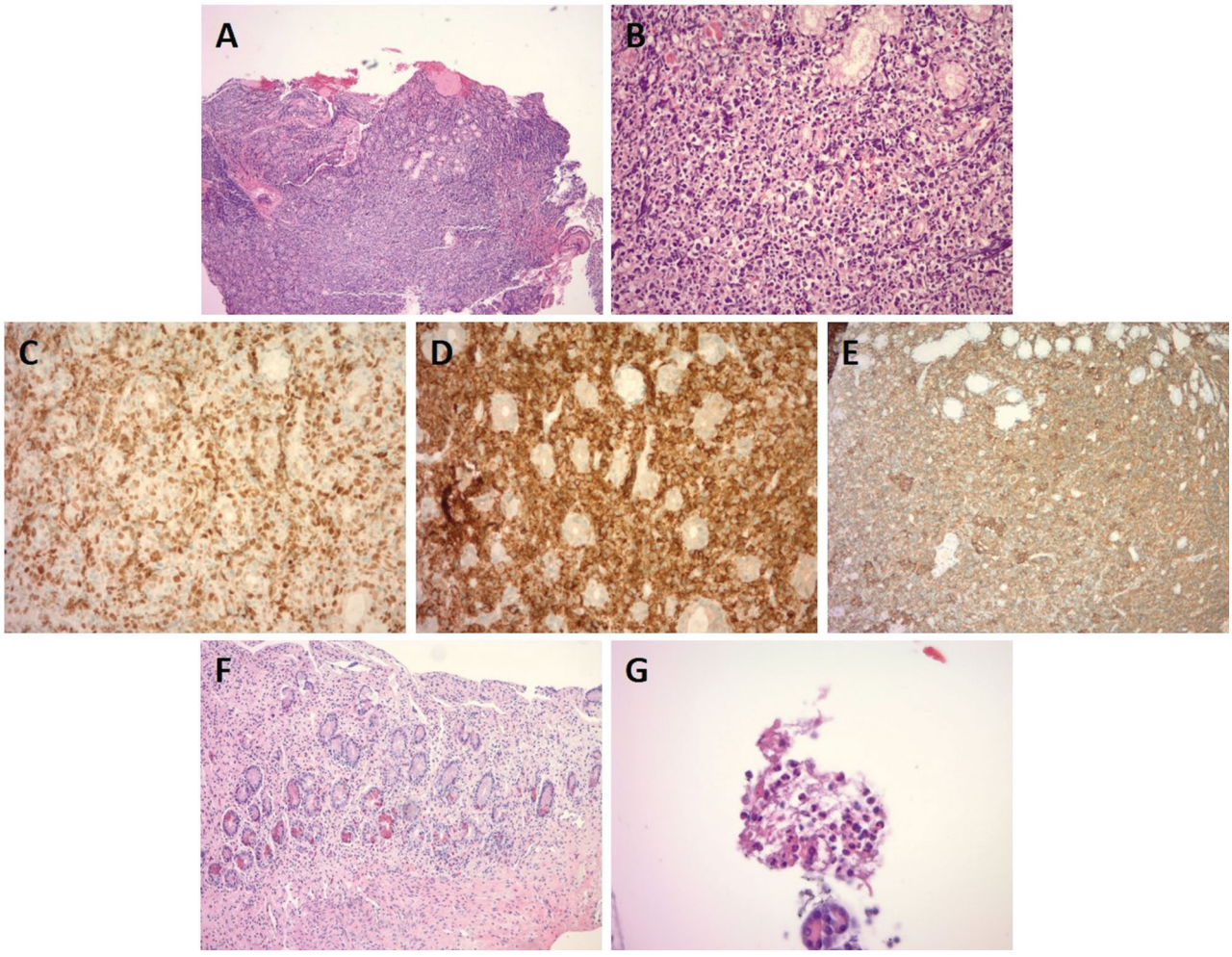


**Figure 2.** Pathology results at diagnosis and after 3 cycles of PVBR. (A,B) Biopsy of the duodenal mass at the time of diagnosis shows duodenal mucosa involved by a diffuse infiltrate of large atypical lymphoid cells with irregular nuclei, vesicular chromatin, prominent nucleoli and a moderate amount of pale cytoplasm. Mitotic and apoptotic figures are frequent with admixed inflammatory cells (A. H&E stain, 40x; B. H&E stain, 200x). (C–E) Immunohistochemistry of the atypical cells at the time of diagnosis are positive for CD20 (C, 200x), MYC (D, 200x) and BCL2 (E, 100x). F. Biopsy of the ulcerated appearing area of the duodenum after 3 cycles of PVBR shows small bowel mucosa with mild chronic inflammation and lamina propria edema (H&E stain, 40x). (G) Fine needle aspiration of the mesenteric mass after 3 cycles of PVBR shows acute inflammatory cells and ghost outlines of necrotic cells (H&E stain, 400x).

as Hodgkin lymphoma [9] since the wide application of immunotherapies, and is best studied in patients treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1/CTLA-4. Such phenomenon is rarely observed in traditional cytotoxic chemotherapy. The proposed mechanisms of pseudoprogression after immunotherapy include extensive infiltration of immune cells, tumor necrosis, intra-lesion hemorrhage and inflammatory response-induced tissue edema [9]. Pseudoprogression of non-Hodgkin's lymphoma (NHL) after CAR T-cell therapy has also been described in recent literature [10,11]. Although histological confirmation is lacking, it is hypothesized that this is also secondary to the systemic/local immune-mediated reaction following CAR T-cell infusion [11]. Very few cases of pseudoprogression following ADCs have been reported to date. In our case, the biopsy of the patient's FDG-avid lesion revealed tissue necrosis, chronic inflammation and edema, consistent with the previously described pathological changes following immunotherapies [12, 13]. Taking into account of the fact that PV can also mediate ADCC as mentioned above [8], we hypothesize that PV-induced pseudoprogression is also an immune-mediated phenomenon. Additionally, tumor flares have been reported in patients with R/R anaplastic large cell lymphoma treated with brentuximab vedotin, an anti-CD-30 ADC that carries the same cytotoxic payload MMAE as PV [14]. Whether the microtubule poison MMAE plays a role in the radiological pseudoprogression will need further investigation.

To our knowledge, this is the second reported case of biopsy-confirmed pseudoprogression of R/R DLBCL to PV-based therapy [15] and the first case of triple-hit DLBCL.

Our clinical observation is particularly important as the encouraging data continue to roll out, the application of PV and other ADCs continues to expand, including in previously untreated DLBCL (NCT01992653, NCT03274492, NCT02257567). It is crucial for clinicians to consider and recognize the atypical radiological and clinical patterns of the early treatment response to PV-based therapy to avoid premature discontinuation of an effective therapy. Short interval scans, advanced biomarkers, such as circulating tumor DNA [16] and prompt diagnostic biopsies may help to discern pseudoprogression and true progressive disease and guide clinical decision making. Modifications of the existing imaging-based response assessment criteria have been proposed in the recent years [17]. It is worth noting that when applied to the PERCIMT (PET Response Evaluation Criteria for Immunotherapy) classification [17], which was developed for patients treated with immune checkpoint inhibitors, imaging findings of our case would not meet criteria for pseudoprogression. This highlights the need for further refinement of the current assessment tools with more novel therapeutic approaches being applied. Beyond traditional morphological and glucose-based imaging, novel nuclear imaging modalities using ligands that directly target key molecules of immune-mediated pathways, such as anti-PD-1 antibody, interferon-γ, protease granzyme B, et al., are under development and may become particularly useful in pretreatment patient selection, response assessment and side effect monitoring [18].

## Disclosure statement

Dr. Jan Cerny serves on the advisory board/consultancy for Jazz Pharmaceuticals and Amgen. He is a Data and Safety Monitoring Board Member for AlloVir, and holds stocks from Actinium Pharmaceuticals, Bluebird Bio Inc., Dynavax Pharma, Atyr Pharmac, Gamida Cell, Miragen Therapeutics, Mustang Bio, Novavax, Ovid Therapeutics, Sorrento Therapeutics, TG Therapeutics, Vaxart Inc, and Veru Inc., outside the submitted work. The other authors have no other conflicts of interest to declare.

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