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LETTER TO THE EDITOR

Low-dose pembrolizumab re-treatment induced complete radiologic and molecular remission in Hodgkin lymphoma recurring from a previous relapse successfully treated by pembrolizumab

Yok-Lam Kwong[1] · Florence Loong[2] · Pek-Lan Khong[3]

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Dear Editor,

The neoplastic Reed-Sternberg (RS) cells in classical Hodgkin lymphoma (cHL) characteristically over-express the programmed cell death ligand 1 (PDL1) and PDL2. Ligation of PDL1 and PDL2 with the inhibitory receptor PD1 on effector T cells is a mechanism by which RS cells escape immunosurveillance. Accordingly, blockade of PDL1/PDL2 binding to PD1 on effector T cells with anti-PD1 antibodies re-establishes anti-lymphoma immunity and is a novel therapeutic strategy for relapsed/refractory cHL [1].

Studies of two anti-PD1 antibodies nivolumab [2] and pembrolizumab [3] in relapsed/refractory cHL showed overall response rates (ORR) of 65–87% and complete response rates (CR) of 16–17%. The optimal post-remission strategies for patients treated with anti-PD1 antibodies have not been defined. Hematopoietic stem cell transplantation (HSCT) is performed for eligible patients. For HSCT-ineligible patients, a continuation of anti-PD1 antibodies is adopted. However, for patients relapsing again after anti-PD1 antibody-induced remission, therapeutic options are limited. Specifically, whether re-treatment with anti-PD1 antibodies may still remain effective is undefined.

✉ Yok-Lam Kwong
ylkwong@hkucc.hku.hk

[1] Department of Medicine, Professorial Block, Queen Mary Hospital, Pokfulam Road, Hong Kong, China

[2] Department of Pathology, Queen Mary Hospital, Hong Kong, China

[3] Department of Diagnostic Radiology, Queen Mary Hospital, Hong Kong, China

A 21-year-old Portuguese man presented in 2013 with stage IIA nodular sclerosis cHL not responding to ABVD (adriamycin, bleomycin, vinblastine, dacarbazine), DHAP (dexamethasone, cytarabine, cisplatin), and bendamustine. Treatment with the anti-CD30 antibody brentuximab vedotin resulted in remission, and an autologous HSCT was performed. He relapsed six months post-HSCT, and re-treatment with brentuximab vedotin and gemcitabine was ineffective. Treatment with low-dose pembrolizumab (100 mg every three weeks, Q3W) resulted in CR. Details up to this point had been included in previous case series [4, 5].

Post-remission maintenance with low-dose pembrolizumab (100 mg Q3W) was administered for two years, with no evidence of recurrence. In March 2018, eight months after cessation of maintenance, he presented with a left chest wall mass and right groin pain. Positron emission tomography computed tomography (PET/CT) scan (point A, Fig. 1) showed hypermetabolic lymphadenopathy in the left infra-clavicular/axillary, subcarinal, right celiac, and right external iliac regions (arrows, Fig. 2a). Biopsy of the left infra-clavicular chest wall lesion showed features of cHL (Fig. 3). Interestingly, the neoplastic RS cells were positive for Epstein-Barr virus (EBV) early RNA (EBER) on in situ hybridization, whereas in all previous biopsies, RS cells were EBER negative. To define the clonal relationship between these relapses, polymerase chain reaction for the immunoglobulin heavy chain gene was performed [6]. Amplification peaks of the 2018 biopsy were identical to those of the 2013 biopsy. Hence, the latest EBV-positive cHL was derived from the previous EBV-negative cHL, excluding the possibility of a new EBV-positive post-transplantation lymphoproliferative disorder. Overall features were consistent with EBV-positive recurrence of a previously EBV-negative cHL.

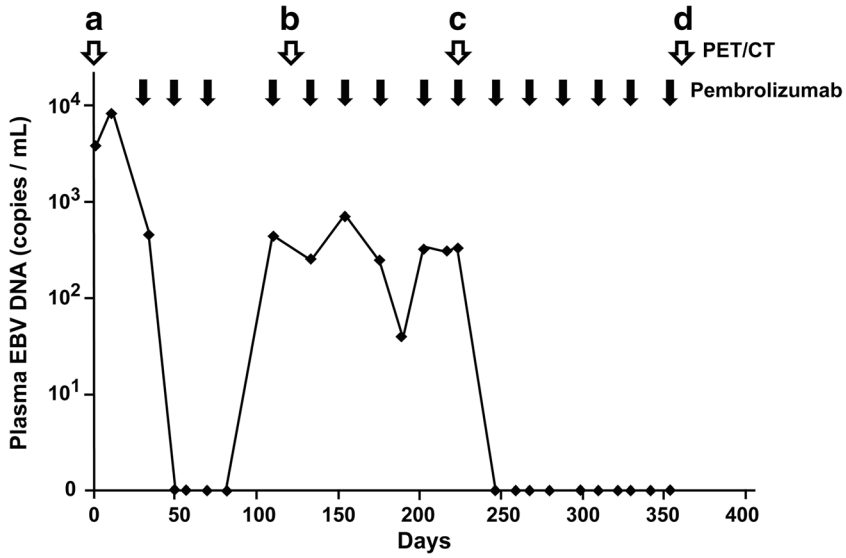

Fig. 1 Time course of changes in plasma Epstein-Barr virus (EBV) DNA and positron emission tomography computed tomography (PET/CT) during pembrolizumab treatment of EBV-positive relapse of classical Hodgkin lymphoma

With informed consent, he was re-treated with low-dose pembrolizumab (100 mg Q3W). As a surrogate biomarker of lymphoma load, plasma EBV DNA was quantified [7]. Before treatment, plasma EBV DNA was elevated to 8.13×10^3 copies/mL (reference value: undetectable) (Fig. 1). After the first dose of pembrolizumab, clinical symptoms abated and there was rapid shrinkage of the left infra-clavicular mass. Plasma EBV DNA fell precipitously to undetectable before the second dose. However, plasma EBV DNA became elevated to 4.45×10^2 copies/mL again before the fourth dose. A PET/CT scan (point B, Fig. 1) was therefore repeated. It showed complete resolution of the subcarinal and celiac lesions, and significant shrinkage of the left shoulder and right external iliac lesions (Fig. 2b, Fig. 4). As there was radiologic improvement, pembrolizumab was continued.

Plasma EBV DNA remained persistently detectable from the fifth to the eighth doses, prompting a repeat PET/CT scan before the ninth dose. At this time, the plasma EBV DNA was increased to 3.3×10^2 copies/mL (point C, Fig. 1). There were new lesions appearing in the left shoulder, with the apparent deterioration of the right external iliac lesion (Fig. 2c, Fig. 4). As he was still asymptomatic, the ninth dose was administered. Interestingly, just before the tenth dose, EBV DNA had become undetectable. After the fifteenth dose (point D, Fig. 1), with EBV DNA remaining persistently undetectable, PET/CT showed complete metabolic response (Fig. 2d, Fig. 4)

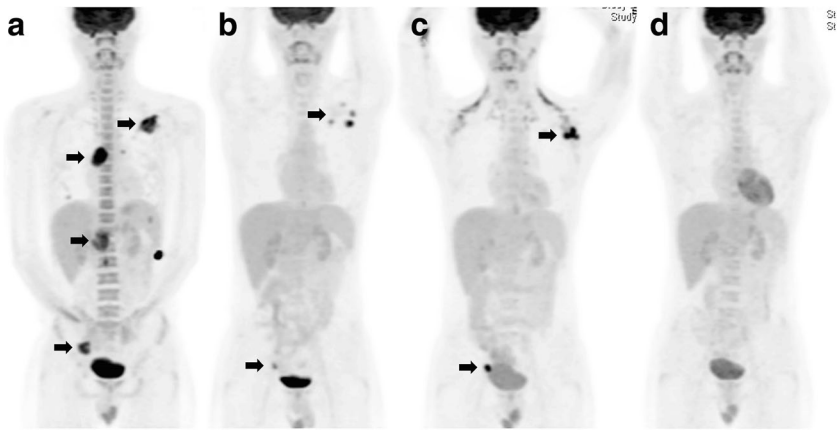

Fig. 2 Serial PET/CT scans during pembrolizumab treatment. The timing of **a** to **d** corresponded to points **a** to **d** in Fig. 1. **a** Hypermetabolic lesions (arrows) before pembrolizumab treatment. **b** Significant improvement in left shoulder and right iliac lesions (arrows), with complete resolution of other lesions. **c** Apparent deterioration of right iliac lesion (arrow), with the appearance of new lesions in the left shoulder (arrow). **d** Complete metabolic response with no hypermetabolic lesions

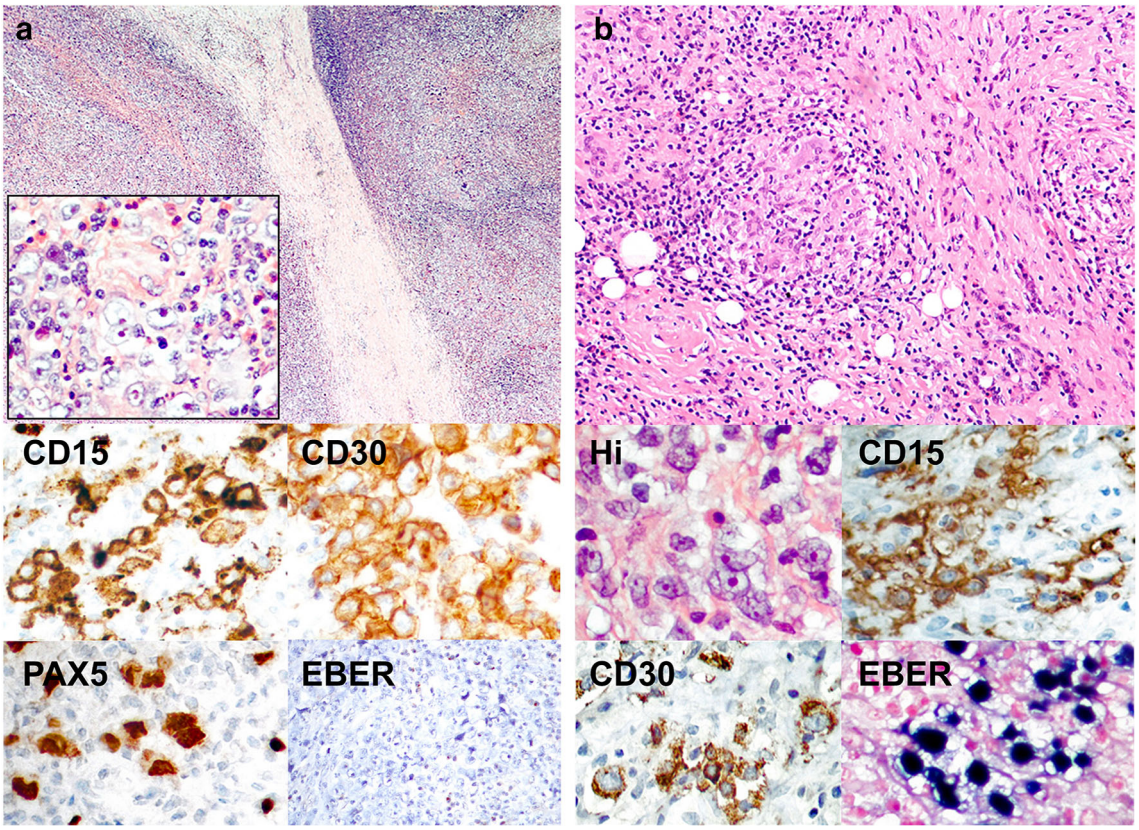

Fig. 3 Histopathologic features of relapsed cHL. **a** Biopsy from 2013. The lymph node was replaced by cellular nodules separated by thick sclerotic bands (hematoxylin eosin, original magnification × 2). High power (× 40) of the nodules (insert) showed a mixed inflammatory background with large sized neoplastic Hodgkin cells and Reed-Sternberg (HRS) cells. Immunohistochemistry showed that the HRS cells were positive for CD15, CD30, and PAX5. In situ hybridization showed that HRS cells were EBER negative. **b** Biopsy from 2018. The nodule showed epithelioid granulomas with mixed inflammatory infiltrates (hematoxylin eosin, original magnification × 2). High power (Hi) (× 40) showed epithelioid granulomas with mixed inflammatory infiltrates and HRS identified patchily. Immunohistochemistry highlighted the HRS cells, which were positive for CD15 and CD30. In situ hybridization showed that the HRS cells were EBER-positive

with resolution of all lesions. Hence, complete radiologic and molecular remission was achieved. He has since received more pembrolizumab, planned for another total of 2 years.

This case provided several important insights into the pathology and treatment of cHL. The present recurrence was EBV-positive. An originally EBV-negative cHL relapsing as an EBV-positive cHL is highly unusual. Conceivably, the immunosuppression consequent on the previous autologous HSCT could have played a role. The depressed immunity might have predisposed the residual RS cells to EBV infection. Alternatively, a small population of EBV-positive RS cells undetected at presentation might have proliferated because of suppressed immunosurveillance. The EBV infection in the RS cells might then in turn have provided the oncogenic impetus for lymphoma recurrence. PDL1 over-expression is intrinsic to RS cells and could be further augmented by EBV infection [8]. The enhanced expression of PDL1 together with putative EBV-derived neo-antigens unrecognizable by existing effector T cells might account for immune escape and lymphoma recurrence. Interestingly, re-treatment with low-dose pembrolizumab remained effective, consistent with our previous observations that low-dose pembrolizumab was highly efficacious in cHL in first relapse [4, 5]. Between the second and third PET/CT scans, there was apparent disease progression. However, continued treatment resulted in complete radiologic and molecular remission; suggesting that the apparent deterioration was due to pseudo-progression [9], a phenomenon known for solid tumors but not well-described in cHL.

In conclusion, pembrolizumab re-treatment was still active for recurrent cHL with a previous relapse successfully treated by pembrolizumab. Finally, this case confirmed once again the efficacy of low-dose pembrolizumab in cHL, at both first and advance relapses.

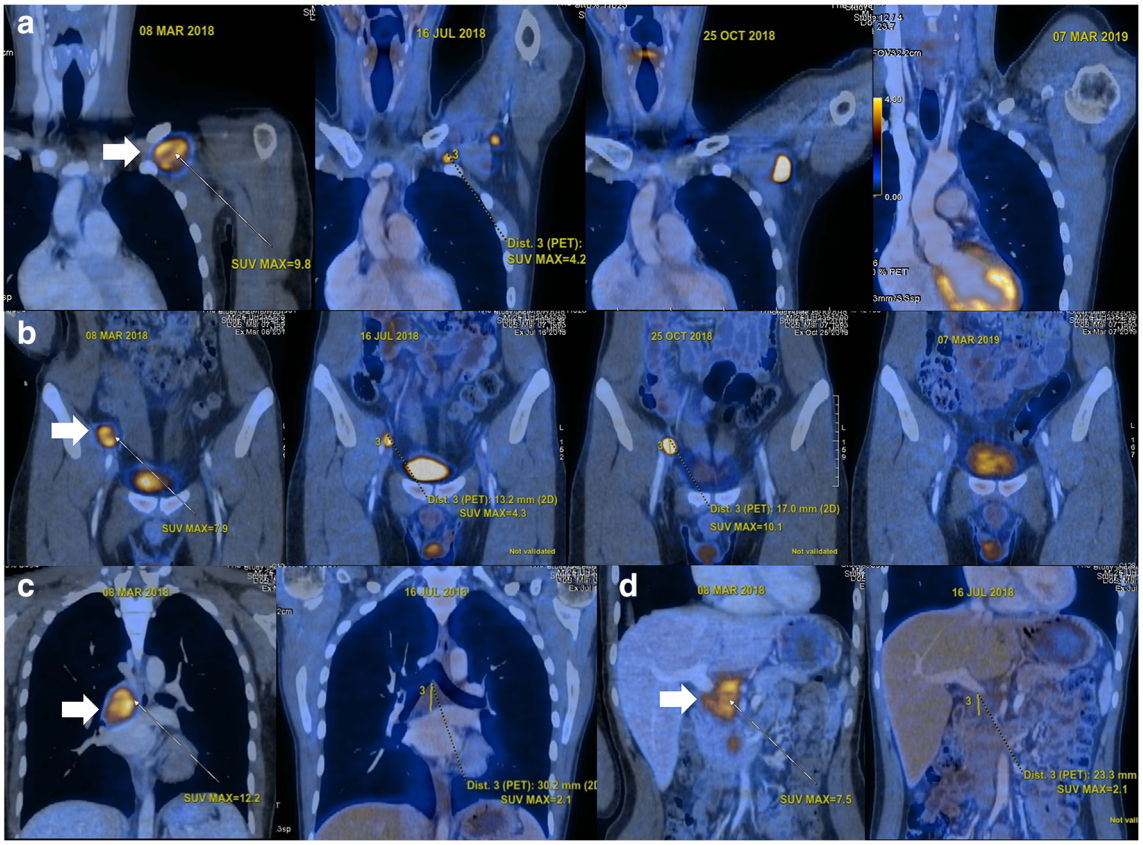

Fig. 4 Changes of hypermetabolic lesions with pembrolizumab treatment. **a** Evolution of left shoulder lesion (arrow) showing improvement and then apparent deterioration followed by complete resolution. **b** Evolution of the right iliac lesion (arrow), which was similar to the left shoulder lesion. **c** Complete resolution of the subcarinal lesion (arrow) after 4 doses of pembrolizumab. It remained undetectable for the rest of the clinical course. **d** Complete resolution of the celiac lesion (arrow) after 4 doses of pembrolizumab. It remained undetectable for the rest of the clinical course

Author contribution Y.L. Kwong: treated the patient and wrote and approved the manuscript

F. Loong: performed the histopathologic diagnosis and wrote and approved the manuscript

P.L. Khong: performed the radiologic diagnosis and wrote and approved the manuscript

Compliance with ethical standards

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

Ethical approval Not applicable.

Informed consent Patient gave informed consent to treatment.

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