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LETTER TO THE EDITOR

Addictive response of primary cutaneous diffuse large B cell lymphoma leg type to low-dose ibrutinib

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Primary cutaneous diffuse large B cell lymphoma leg type (PCLBCL-LT) is a rare malignancy occurring predominantly below the knee, but may involve other cutaneous and extracutaneous sites [1]. Lymphoma cells typically express CD20, CD79A, BCL2, BCL6, MUM-1, and FOXP1, but not CD10 [1, 2]. Gene expression of PCLBCL-LT resembled activated B cell diffuse large B cell lymphoma (ABC-DLBCL). Consequently, genes involved in NF-κB activation were frequently mutated [3], with the *MYD88* L265P mutation most prevalent, found in 60–80% of cases [3].

Outcome of PCLBCL-LT is unfavorable. Pre-rituximab, the 5-year overall survival (OS) was about 50%, with few survivals beyond 10 years [2, 4]. With rituximab-containing regimens, 5-year survivals were improved to about 75% [4]. Poor risks affecting 5-year OS included disseminated disease (solitary versus disseminated: 70% versus 0%) [5], BCL2 expression (positive versus negative: 41% versus 89%) [6], and *MYD88* status (L265P versus wildtype: 41% versus 89%) [7].

A 56-year-old Brazilian man presented in October 2013 with left arm lesions, histologically showing large CD20+, BCL2+, BCL6+, and FOXP1+ lymphoma cells. Positron emission tomography computed tomography (PET/CT) showed skin lesions restricted to the left arm. However, bone marrow was involved (Fig. 1A). Overall features were consistent with stage IV PCLBCL-LT. Six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) were given, leading to PET/CT-confirmed complete response (CR), and biopsy-confirmed marrow remission.

Six months later, relapse at the original sites occurred (Fig. 1B). Lesions resolved with involved-field radiotherapy. Six months later, biopsy-proven relapse occurred again (Fig. 2A, B). Marrow biopsy was normal. Because of slow disease progression, he was treated with obinutuzumab (1000 mg/dose × 4 two-weekly doses) and oral chlorambucil (2 mg/day). Lesions remained stable.

In January 2016, arm lesions progressed (Fig. 2C, D). With informed consent, lenalidomide (10 mg/day) was started. Within 4 weeks, there was substantial improvement (Fig. 2E, F). Four months afterwards, forearm lesions had entirely subsided, but upper arm lesions persisted.

In May 2016, fleshy lesions re-appeared in the upper arm (Fig. 3A). He opted for surgery, and resected lesions were confirmed to be lymphomatous. In August 2016, lesions recurred again (Fig. 3B).

The biopsy before radiotherapy was retrieved for *MYD88*, *CD79A*, and *CD79B* sequencing. Two mutations were found, *MYD88* L265P and *CD79B* Y169S (Fig. 1C), both hotspot mutations in DLBCL. These findings suggested that Bruton tyrosine kinase (BTK) inhibition might be effective. In September 2016, lesions were more obvious (Fig. 3C, D). With informed consent, he received low-dose ibrutinib (140 mg/day). The lesions entirely resolved in 4 weeks (Fig. 3E). In April 2017, with no lesions found clinically (Fig. 3F), PET/CT scan confirmed metabolic CR. Low-dose ibrutinib was continued.

In February 2019, in CR for nearly 30 months, he went on a holiday and ran out of ibrutinib. Skin lesions recurred 3 days after stopping ibrutinib (Fig. 4A). Three weeks after stopping ibrutinib, full-blown relapse occurred on the arm (Fig. 4B), with similar lesions on his left flank and hip (Fig. 4C). On follow-up in March 2019, a biopsy confirmed relapse. Ibrutinib was resumed at 140 mg/day. Lesions totally disappeared in 4 weeks (Fig. 4D, E). As of May 2019 (Fig. 4F), he has remained in CR.

This case had all the unfavorable characteristics, including disseminated disease, BCL2 positivity and *MYD88* L265P

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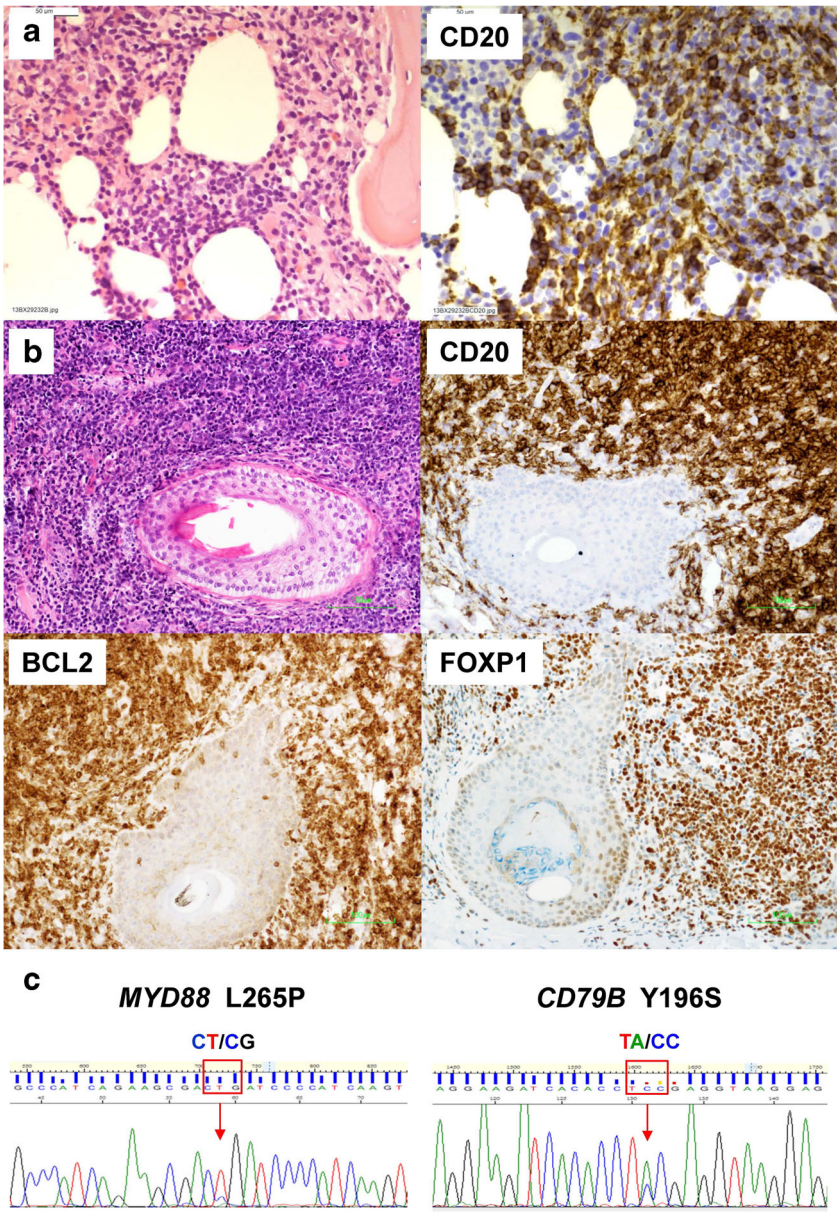

Fig. 1 Histopathologic and genetic features of PCLBCL-LT. **A** Bone marrow trephine biopsy, with diffuse infiltration of the marrow by CD20-positive medium-sized abnormal lymphoid cells (original magnification 200×). **B** Skin biopsy, showing infiltration around a hair follicle of medium- to large-sized abnormal lymphoid cells that were positive for CD20, BCL2 and FOXP1 (original magnification 200×). **C** Sanger sequencing showing *MYD88* L265P and *CD79B* Y196S mutations. Only the forward sequences are shown. Backward sequences confirmed the same mutations

mutation. He had short-lived responses to multiple regimens. Based on the importance of NF-κB activation in PCLBCL-LT, he was treated with low-dose lenalidomide, and achieved a partial response. Interestingly, transient partial response to lenalidomide had previously been reported in refractory PCLBCL-LT [8].

His response to ibrutinib was most remarkable. Owing to affordability, the lowest practical daily dose of 140 mg (one tablet) was used, as ibrutinib was not reimbursed for lymphoma therapy. This dose is only one-quarter of that used for mantle cell lymphoma and marginal zone lymphoma (560 mg/day), and one-sixth of that used for central nervous system B cell lymphoma (840 mg/day). Even at this low dose, ibrutinib induced a swift CR. During remission, whether ibrutinib could be stopped was unclear. This issue was addressed when the patient became complacent and ran out of drug. Despite a CR for over 2 years, stopping ibrutinib for just a few days was enough to lead to disease recurrence. Re-treatment with low-dose ibrutinib resulted in another prompt CR. Hence, this case of PCLBCL-LT was addicted to ibrutinib treatment. During remission, ibrutinib suppressed but did not eradicate the lymphoma, similar to ibrutinib therapy for other lymphoid malignancies.

In ABC-DLBCLs with mutant *MYD88* and *CD79,* there is chronic active B cell receptor (BCR) signaling. Pharmacological inhibition of BTK, a key molecule downstream of BCR, may therefore be effective [9]. In fact, for relapsed/refractory ABC-DLBCL harboring both *MYD88* and *CD79B* mutations, ibrutinib therapy (560 mg/day) had been reported to result in an overall response rate of 80% [9].

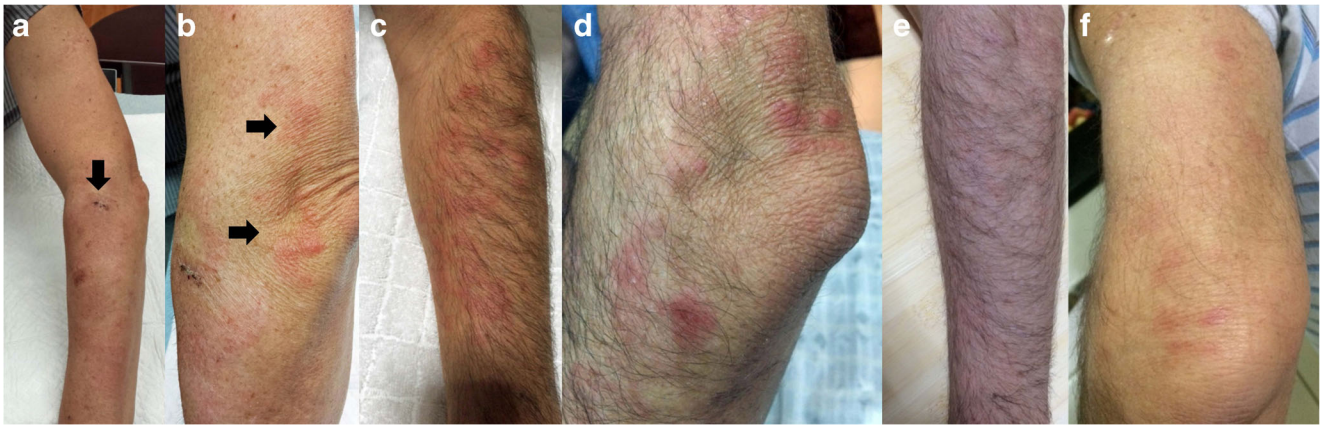

Fig. 2 Evolution of arm lesions during lenalidomide therapy. **A** and **B** Photographs taken in May 2015, showing subtle recurrence of lymphoma after radiotherapy. **A**: Left forearm. Note the faint discolorations in the forearm, one of which was biopsied (arrow), showing lymphomatous infiltration; **B**: More obvious skin infiltration in the upper arm (arrows). **C** and **D**. Progression of lymphoma despite obinutuzumab and chlorambucil therapy. Photographs taken in January 2016, immediately before commencement of lenalidomide therapy. **C**: Progression of disease in the forearm; **D**: Lymphomatous lesions were obvious in the upper arm. **E** and **F**. One month after lenalidomide therapy, with photographs taken in February 2016. **E**: Total disappearance of forearm lesions; **F**: Minimal residual lesions in upper arm

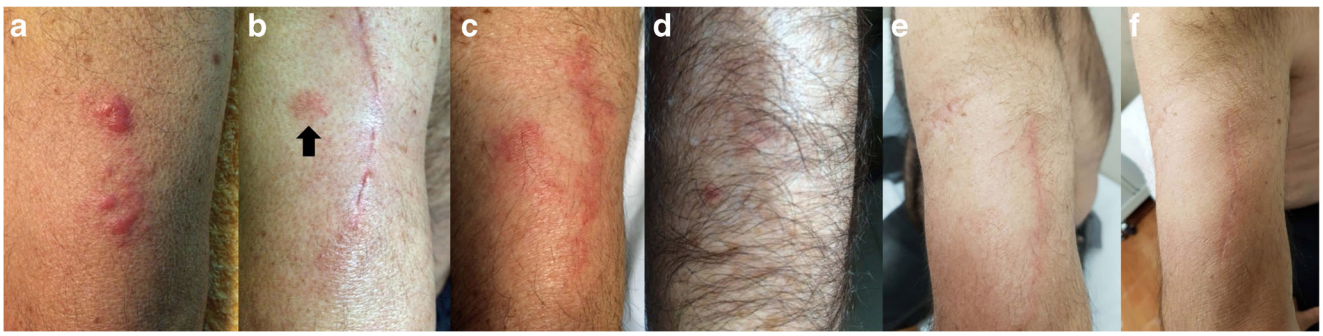

Fig. 3 Evolution of arm lesions during ibrutinib therapy. **A** Progression of upper arm lesions despite lenalidomide therapy (May 2016). **B** Previous lesions were totally resected. However, subtle lesions (arrow) started to appear next to the surgical scar (August 2016). **C** and **D** Photographs taken in September 2016, immediately before ibrutinib therapy. **C** More obvious lesions in the upper arm, with infiltration of the surgical scar; **D** Obvious lesions in the forearm. **E** Total disappearance of skin lesions after 1 month treatment with ibrutinib at 140 mg/day (October 2016). **F**. Maintenance of remission while on ibrutinib (April 2017)

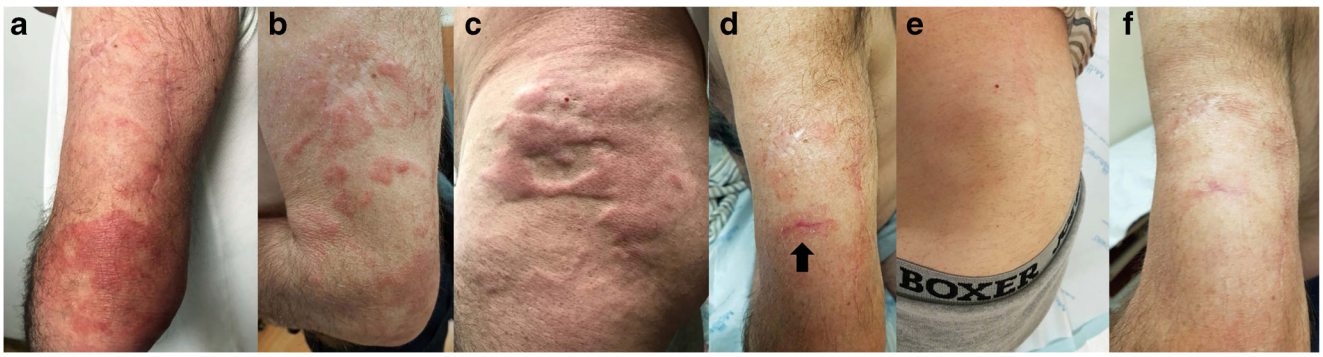

Fig. 4 Relapse within a short time of stopping ibrutinib, and rapid response after re-treatment with ibrutinib. **A** Recurrence of skin lesions 3 days after stopping ibrutinib. Photograph (March 8, 2019) provided by patient. **B** More obvious recurrence of upper arm lesions 23 days after stopping ibrutinib. Photograph (March 28, 2018) provided by patient. **C** Lesions on left flank and hip. Photograph (March 28, 2018) provided by patient. **D** Complete resolution of the upper arm lesions after 4 weeks of ibrutinib re-treatment (April 24, 2019). Note the surgical scar (arrow) indicating the biopsy that proved disease recurrence. **E** Resolution of the flank and hip lesions, with residual discoloration (April 24, 2019). **F** Maintenance of continuous response at the latest follow-up (May 28, 2019)

It was recently shown that 35% of PCLBCL-LT harbored concomitant *MYD88* and *CD79B* mutations [7]. As shown in this case, concomitant *MYD88* and *CD79B* mutations were observed, coinciding with an excellent response to ibrutinib. In other lymphoid malignancies, ibrutinib dosages ranging from 420 to 840 mg/day appeared necessary for therapeutic efficacy, as dose reduction or non-compliance results in inferior outcome [10]. Hence, the high efficacy of ibrutinib at 140 mg/day reflects a genuine extraordinary sensitivity of this case of PCLBCL-LT to ibrutinib.

Author contribution A. Pang: performed the investigations, wrote and approved the manuscript.

R. Au-Yeung: performed the pathologic analysis, wrote and approved the manuscript.

R. Leung: performed the pathologic analysis, wrote and approved the manuscript.

Y.L. Kwong: treated the patient, 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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