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Letter to the Editor

Eight-cycle rituximab therapy resulted in complete remission in primary cutaneous marginal zone lymphoma

Primary cutaneous marginal zone B-cell lymphoma (PCMZL) is a low-grade malignant B-cell lymphoma that presents in the skin, with no evidence of extracutaneous localizations at the time of diagnosis. This type of lymphoma is 2–16% of all the cutaneous lymphomas [1]. Previously, these lymphomas were designated as primary cutaneous immunocytomas. But recently, this term was replaced by primary cutaneous marginal zone B-cell lymphoma. Also, in the new WHO–EORTC classification, the term PCMZL is used for cutaneous lymphomas [2]. PCMZL usually has an indolent clinical course with an estimated disease-specific 5-year survival rate exceeding 95%. Although the clinical course is generally favorable, recurrence rate following the initial treatment is high and varies between 25% and 68% [3]. PCMZLs have a tendency to recur in the skin, and also the involvement of extracutaneous sites is exceedingly rare [4]. However, in the recent studies, extracutaneous dissemination and even death due to lymphoma have been reported [5]. In the treatment planning, the clinical presentation, such as the multifocal appearance together with the indolent course of the disease, has to be carefully considered. There are several treatment modalities like close observation, radiation therapy, surgical excision, topical medications, or systemic therapies [2,6–8] but bear the risk of relapse and/or esthetic impairment.

Rituximab is a chimeric human/mouse anti-CD 20 monoclonal antibody that has emerged in recent years as an effective therapy for NHL and other B-cell malignancies. It has been approved for use in combination with cyclophosphamide, doxorubicine, vincristine and prednisolone (CHOP) chemotherapy regimen for the treatment of aggressive NHL [9]. Recently, rituximab has also been given consideration in the treatment of CD 20 (+) PCMZL systemically, albeit in small patient collectives and case reports with satisfactory results (Table 1).

Herein we described, a patient with PCMZL who is an active hepatitis B patient treated with extended rituximab schedule. To our knowledge, this is the first case with PCMZL treated with eight course weekly rituximab although the case was active HBs Ag.

37-Year-old man presented with a 2-year history of progressive erythematous nodules localized on the back, lomber region, the left gluteus and the right femoral lateral region. A total of 5 lesions, 1–6 cm in size, were counted. He had no fever, weight loss or night sweats. Physical examination did not reveal any enlargement of the regional lymph nodes. Hepatosplenomegaly was not noted. Blood counts and morphology were normal. Routine biochemical profile was within the normal limits, except for an elevated ALT level (67 U/l), the positivity of HBs Ag and an increased HBV DNA level (19,432 copy/ml with 3470 UI/ml). Liver USG was normal. Histopathological examination of skin biopsy from the lomber region showed that there was a lymphoid proliferation in coarse centroblastic cells at the intermediate consisting of centrocytical cells with mediate magnitude forming infiltration with nodular style at dermis and subcutaneous fatty tissue. Immunohistochemical staining revealed positivity for CD 20, CD 45 RO, CD 23, whereas CD 10, cycline D1, BCL 6 were negative (Fig. 1A,B,C,D). Scattered CD 3 and CD 5 positivity were also observed in lymphocytic infiltrate. κ-Light chain and λ-light chain were scantly positive in plasma cells. Both histopathological and immunophenotypical examination of the bone marrow aspiration and biopsy specimens did not reveal any evidence of the disease. The diagnosis of PCMZL was made with the clinical presentation, the immunohistological findings, and the absence of extracutaneous involvement by extensive systemic workup. Firstly, treatment with lamivudine 100 mg/day PO was initiated for hepatitis B. After 1 month, the multifocal localization and the strong CD 20 positivity prompted us to use rituximab, as a single agent, at the dosage of 375 mg/m^2 once a week as an intravenous infusion in 1 l of normal saline. After 4 weeks, two lesions disappeared and the others were partially regressed (> or =50% reduction of all the measurable lesions). However, we obtained a complete response for all the lesions after 6 weekly cycles of rituximab. And the treatment was completed to 8 weeks. Control HBV DNA level was returned to the normal limits (<2000 copy/ml with <357 UI/ml) and the value of liver function tests were also normalized. At present, 15 months after rituximab therapy, the patient was in complete remission with normal liver function tests under lamuvidine treatment.

For the PCMZL, the optimal management is less clear and therapeutic decisions vary individually. While a watch-and-wait policy might initially be adopted in some patients, localization of the lesions may warrant therapy due to esthetic impairment and the patient's consecutive wish for therapy even in the absence of an aggressive clinical course. The clinical presentation with a high percentage of multilocular lesions, the high recurrence rates and the potential for local recurrences within the same anatomic site indicate the requirement for a potent long-acting therapy devoid of toxic side effects.

As seen in Table 1, there are 15 cases with PCMZL treated with systemic single-agent rituximab in the literature. Ten out of these patients had received four cycles, while 2 patients had received six and 4 patients eight cycles of rituximab therapy. Two patients (cases 5 and 6) had received an additional treatment. Of the 10 patients who had received therapy for a period of 4 weeks, 5 had CR, 3 had PR, 1 had PD and 1 had SD, and 5 patients were alive with no evidence of the disease, whereas 5 patients survived with the disease. Among the patients who had received therapy for a period of 6 weeks, case 5 was alive with no evidence of the disease with an additional 2-week rituximab and local RT for 48 months and case 9 relapsed in the 29th month after CR, and had remained in remission for 94 months, but it was not reported what they were administered for recurrence. This series is too small to allow for extrapolation of the optimal duration of therapy and this aspect warrants further

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Table 1
Summary of patients with cutaneous marginal zone lymphoma treated with rituximab as reported in the literature.

Author	Case no.	Sex/age	Lesion (single or multifocal)	No. of treatment cycles (375 mg/m^2/weekly)	Response/time to relapse (mo)	Therapy following recurrent	Follow-up (mo)/status
Valencak et al. [10]	1	F/44	Multiple	Four	CR	–	10/NED
	2	M/68	Multiple	Four	CR/11	R (8 cycle)	53/NED
	3	M/51	Multiple	Four	CR/7	R (4 cycle), excision (three more periods of recurrent disease)	75/NED
	4	M/54	Multiple	Four	CR	–	28/NED
	5	M/37	Multiple	Six	PR	Additional treatment[a]	48/NED
Morales et al. [11]	6	F/38	Multiple	Four	PR	Additional treatment[b]	21/AWD
	7	F/75	Multiple	Four	SD/NA	–	40/AWD
	8	F/64	Multiple	Four	PR/2	NR	5/AWD
	9	M/68	Multiple	Six	CR/29	NR	94/NED
	10	M/58	Multiple	Four	PD/NA	–	3/AWD
Kerl et al. [12]	11	F/70	Single	Four	CR	–	24/NED
Gellrich et al. [13]	12	M/48	Multiple	Eight	CR/23	–	NR
Soda et al. [14]	13	M/38	Multiple	Four	PR	–	6/AWD
Gellrich et al. [15]	14	NR/74	Multiple	Eight	CR	–	7/NED
	15	M/49	Multiple	Eight	CR	[c]	9/NED
Present case	16	M/37	Multiple	Eight	CR	–	13/NED

AWD, alive with disease; CR, complete response; F, female; M, male; NA, not applicable; NED, alive with no evidence of disease; NR, not reported; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease.

[a] Rituximab (2 cycles) and local RT.

[b] Rituximab (4 cycles) (1 weekly infusion × 4) every 6 months.

[c] Rituximab 2 × 4 iv infusions weekly w/6 subsequent iv infusions every 4 weeks plus perilesional injections.

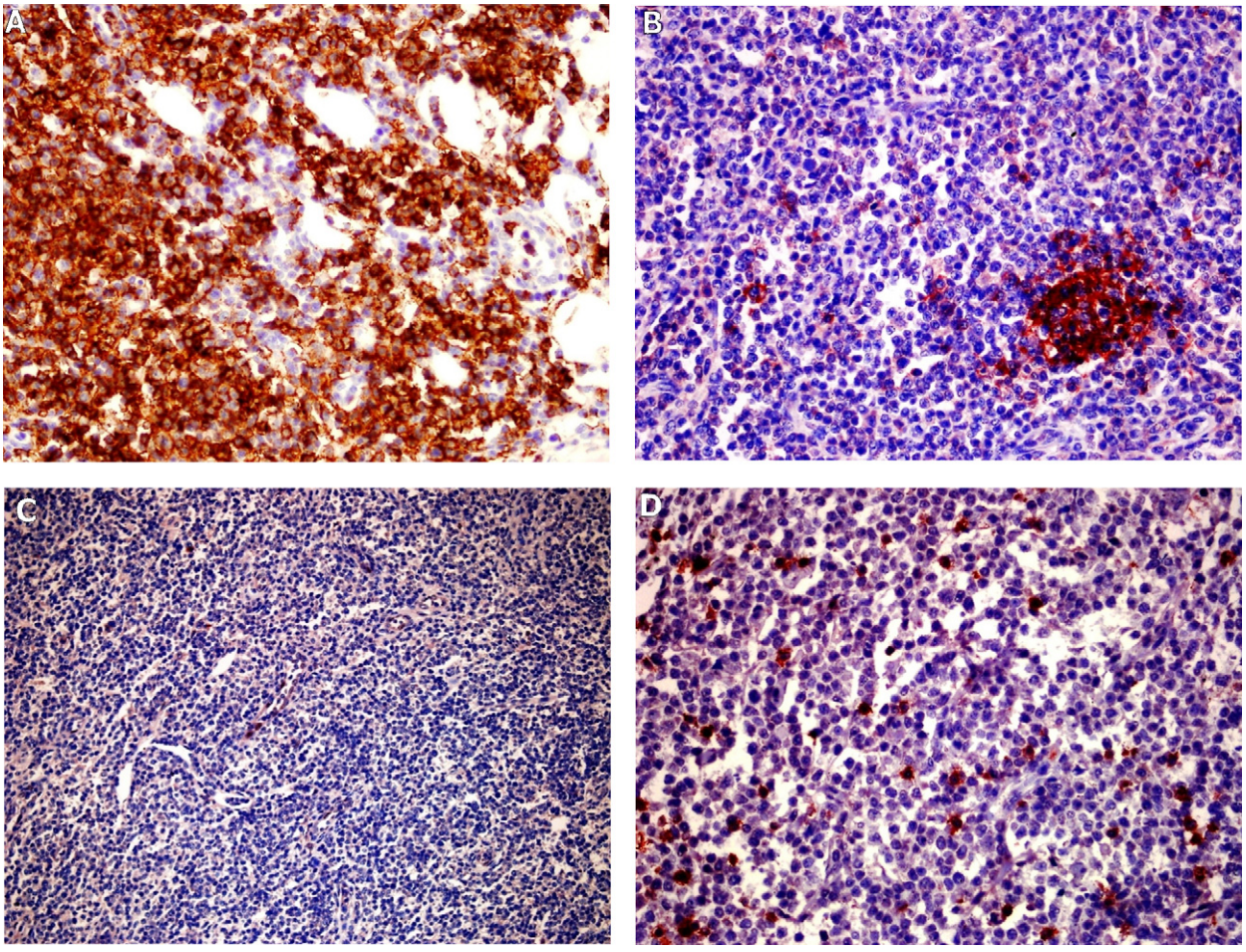

Fig. 1. (A) CD 20 positivity neoplastic lymphoid cells (×40); (B) CD 23 negative lymphoid cells (×40); (C) Cyclin D1 negative foliculer dentritic cells (×20); (D) CD 3 was positive in dispersed mature lymphoid cells (×40).

evaluation in the future. In our opinion, it might be appropriate that the related patients should be administered with rituximab in two more weeks, even after full remission was observed. We administered a therapy with lamivudin treatment during 8 weeks to our patient, as the patient was in partial remission 4 weeks later and he preferred the treatment of all of his lesions. Since the patient had multiple lesions, we did not consider radiotherapy. All of the lesions disappeared at the end of the 6-week therapy. In the light of the letters indicating that the extended rituximab would be more effective [13,16,17], we administered the therapy to the patient for a period of 8 weeks.

Reactivation of hepatitis B virus (HBV) infection is a well-recognized and potentially fatal complication in infected patients treated with chemotherapy for lymphoid malignancies [18]. HBV reactivation has been increasingly reported since the introduction of rituximab. There is an increasing number of reports concerning patients receiving rituximab either as monotherapy or in combination with chemotherapy, whose viral reactivation might cause significant liver damage in inactive carriers [19]. Lamivudine is a potent reverse transcriptase inhibitor which has a high efficacy in inhibition of viral replication. It has been approved as an antiviral treatment in hepatitis-B-infected patients. Li et al. showed that the preemptive use of lamivudine successfully reduced the incidence and severity of hepatitis in HBV carriers, who received rituximab-containing regimen for lymphoma [20]. There is no evidence in the literature to indicate how long the prophylactic lamivudine therapy should be used after the completion of rituximab. The American Association of Study of Liver Diseases recommends prophylaxis with lamivudine for 6 months after the completion of immunosuppressive therapy or chemotherapy for HBsAg-positive patients receiving rituximab-containing regimens [21]. Consequently, some authors advise that prophylaxis should be continued for at least 1 and possibly 2 years after the discontinuation of chemotherapy in HBsAg-positive patients [22]. And also, delayed HBV reactivation after lamivudine treatment was reported [23], so we planned to use it for a period of 2 years after the rituximab treatment.

In conclusion, in PCMZL and the other mucosa associated lymphoid tissue (MALT) lymphoma, we do not know the optimal duration of rituximab as a single agent but, we observed that a therapy of eight cycles with rituximab is safe and successful in a patient with PCMZL and hepatitis B under lamivudine treatment.

Conflict of interest

None.

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