Clinicopathologic and genetic features of primary cutaneous B-cell lymphoma

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CHAPTER 3

Primary cutaneous marginal zone B-cell lymphoma. Clinical and therapeutic features in 50 cases

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OBSERVATION

Primary Cutaneous Marginal Zone B-Cell Lymphoma

Clinical and Therapeutic Features in 50 Cases

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Background: Primary cutaneous marginal zone B-cell lymphoma (PCMZL) is a low-grade B-cell lymphoma that originates in the skin, with no evidence of extracutaneous disease. Studies focusing on the optimal treatment of PCMZL have not been published thus far. We describe 50 patients with PCMZL to further characterize clinical characteristics and outcome and, in particular, to evaluate our current therapeutic approach.

Observations: The majority of the patients (36/50 [72%]) presented with multifocal skin lesions, and 14 patients (28%) presented with solitary or localized lesions. The initial treatment of patients with solitary lesions consisted of radiotherapy or excision, whereas patients with multifocal lesions received a variety of initial treatments, most commonly radiotherapy and chlorambucil therapy. Cutaneous relapses developed in 19 (48%) of 40 patients who had complete remission and were more common in patients with multifocal disease. After a median period of follow-up of 36 months, 2 patients developed extracutaneous disease, but none of the patients died of lymphoma.

Conclusions: Patients with PCMZL who have solitary lesions can be treated effectively with radiotherapy or excision. For patients with PCMZL who have multifocal lesions, chlorambucil therapy and radiotherapy are suitable therapeutic options. In case of cutaneous relapses, the beneficial effects of treatment should carefully be weighed against the potential adverse effects.

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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.[1] This type of lymphoma has been reported to represent 2% to 16% of all cutaneous lymphomas.[1,2] Previously, these lymphomas were designated as *primary cutaneous immunocytomas*, but in recent years, the term *primary cutaneous marginal zone B-cell lymphoma* has been preferred. Also, in the new World Health Organization–European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas, the term *PCMZL* is used.[3] Primary cutaneous marginal zone B-cell lymphomas are characterized by a clonal proliferation of small B lymphocytes, including marginal zone (centrocyte-like) cells, lymphoplasmacytoid cells, and plasma cells showing monotypic cytoplasmic immunoglobulin light-chain expression on paraffin sections. The small neoplastic B cells have a Bcl-2$^+$, Bcl-6$^-$, CD10$^-$ phenotype, which facilitates differentiation from primary cutaneous follicle center lymphomas and cutaneous lymphoid hyperplasias (pseudolymphomas).[4,5] Recent genetic studies identified the presence of specific genetic aberrations, including the chromosomal translocation t(14;18)(q32;q21), involving *IGH* (the immunoglobulin heavy-chain locus) and the gene for mucosa-associated lymphoid tissue 1 (*MALT1*) or a trisomy 18, in a minority of these lymphomas.[6,7] As a result of the widespread use of gene rearrangement analysis and immunohistochemical studies, increasing numbers of PCMZLs are now being recognized.

Initial studies on PCMZLs (or primary cutaneous immunocytomas) emphasized their indolent clinical behavior and excellent prognosis.[8,9] It was found that PCMZLs have a tendency to recur in the skin, but dissemination to extracutaneous sites was considered exceedingly rare.[8-11] However, in recent studies, extracutaneous dissemination and even death due to lymphoma have been reported more often.[12,13] Apart from case reports and small series of patients, studies specifically addressing the optimal treatment of PCMZL

have not been published. Radiotherapy and surgical excision have been suggested as preferred treatments in patients with solitary or localized skin lesions, but published data on the treatment of patients with multifocal skin lesions are rare.[1]

In the present article, we describe the results of a retrospective analysis of 50 cases of PCMZL. The goal of our study was to further characterize the clinical characteristics and clinical outcome and, in particular, to evaluate our current therapeutic approach for this type of cutaneous B-cell lymphoma.

METHODS

Between 1985 and July 2004, a total of 62 patients with a diagnosis of PCMZL were included in the registry of the Dutch Cutaneous Lymphoma Working Group, Amsterdam, the Netherlands. Patients whose follow-up was shorter than 12 months (n=7) and patients in whom staging procedures had been incomplete (n=5) were excluded. The final study group included 50 patients with a definite diagnosis of PCMZL according to the criteria of the World Health Organization–European Organization for Research and Treatment of Cancer classification for primary cutaneous lymphomas.[3] None of the patients showed evidence of extracutaneous disease at the time of diagnosis, as assessed by adequate staging procedures, including complete blood cell counts, computed tomography of the chest and abdomen, and a bone marrow biopsy. Clinical, follow-up, and therapeutic data on all 50 patients were gathered from the files of the Dutch Cutaneous Lymphoma Working Group, from medical records, and from communication with the patients' physicians.

RESULTS

CLINICAL CHARACTERISTICS

Information on clinical presentation, type of initial treatment, response to therapy, and follow-up data are presented in **Table 1** and **Table 2**. **Figure 1** shows the characteristic clinical presentation of 2 patients with PCMZL. B symptoms were always absent. One patient had a history of an associated autoimmune disease (systemic lupus erythematosus) before she developed PCMZL. In 5 (20%) of the 25 patients tested, antibodies against *Borrelia burgdorferi* were found. In 1 of the 5 patients, the skin lesions developed in a preexisting area of acrodermatitis chronica atrophicans. In another patient, the skin lesions developed on the upper part of the left arm in an area where he had received a hepatitis A vaccination 6 months earlier.

THERAPEUTIC CHARACTERISTICS

Data on initial treatments of the patients are presented in **Table 3**. Solitary or localized skin lesions were treated with either surgical excision (n=8) or local radiotherapy (n=6) with doses varying between 2000 and 4000 rads (20 and 40 Gy), which resulted in a complete remission in all but 1 case (patient 7). In patient 7, who presented with a 6-year-history of slowly progressive perioral skin tumors that were histologically characterized by an almost pure population of IgG-λ–positive plasma cells, radiotherapy appeared ineffective (**Figure 2**). Subsequent excision of many small tumors around the patient's mouth resulted in an acceptable cosmetic appearance.

The 36 patients who presented with multifocal skin lesions had received a wide variety of treatments (Table 3). In general, the patients who presented with only a few skin lesions had been treated with either local radiotherapy (n=11) or surgical excision (n=2), which had resulted in a complete remission in all of them. Patients received radiotherapy in 2 or 3 fields, with doses varying between 1200 and 3000 rads (12 and 30 Gy) in 9 patients and a dose of 4000 rads (40 Gy) in only 2 patients.

Eleven patients who generally had more widespread disease were treated with chlorambucil (4-10 mg) over a median period of 16 weeks (range, 8-23 weeks). Six (55%) of 11 patients reached a complete remission after a median treatment period of 13 weeks; 4 patients had a partial remission, with 50% to 80% improvement; and 1 patient (No. 37) showed disease progression, with involvement of multiple lymph nodes. No serious adverse effects were observed, except for a case of lymphocytopenia after 16 weeks in 1 patient (No. 40) with schizophrenia who simultaneously used clozapine (Leponex), which may also be associated with lymphocytopenia.[14]

Five patients were initially treated with multiagent chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (n=3) or cyclophosphamide, vincristine, and prednisone (COP) (n=2), resulting in a complete remission in 4 patients. However, in all 4 patients, the disease relapsed after the last course of chemotherapy. Three of the 5 patients had undergone multiagent chemotherapy because of an initial diagnosis of primary cutaneous follicle center lymphoma, which was reclassified as PCMZL because of the availablility of new markers.[4,5]

Finally, it should be mentioned that before one of these initial treatments was started, all 5 patients with a positive *Borrelia* serologic test result had been treated with antibiotics (doxycycline, 100 mg twice a day for 1 month), without therapeutic benefit.

CLINICAL COURSE AND FOLLOW-UP

After initial treatment, 40 (80%) of 50 patients reached a complete remission, including 13 (93%) of 14 patients who presented with solitary or localized disease and 27 (75%) of 36 patients who presented with multifocal skin lesions. Nineteen of these 40 patients developed 1 (n=10) or multiple (n=9) cutaneous relapses after an estimated median disease-free interval of 11 months (range, 2-114 months). Skin relapses after local radiotherapy (n=9/16) were always outside the previously irradiated skin area. A cutaneous relapse occurred in 16 (59%) of 27 patients who presented with multifocal disease, compared with 3 (23%) of 13 patients who presented with solitary or localized skin lesions (log-rank test, $P=.04$). The estimated 5-year relapse-free survival rates after complete remission were 39% and 77%, respectively (**Figure 3**). Other clinical parameters, including type of initial treatment, age at diagnosis, and sex, were not correlated with the development of a (cutaneous) relapse after complete remission (data not shown).

Table 1. Clinical Characteristics in 50 Cases of Primary Cutaneous Marginal Zone B-Cell Lymphoma

Patient No./ Sex/Age, y	Clinical Presentation	History of Skin Lesions Before Diagnosis, mo	Initial Treatment	Response	Relapse After CR	Follow-up, mo
1/M/55	2 Localized nodules on left upper arm area	1	Excision	CR	No	144 (AND)
2/M/38	Solitary nodule in right knee cavity	24	Excision	CR	No	48 (AND)
3/F/48	Solitary tumor on right shoulder	5	Excision	CR	Skin	47 (AND)
4/M/45	Solitary tumor on abdomen	36	Excision	CR	No	16 (AND)
5/M/55	Solitary tumor on right lower arm area	12	Excision	CR	No	54 (AND)
6/M/49	Solitary tumor on right upper arm area	1	Excision	CR	Skin	30 (AND)
7/M/54	Perioral localized tumors	Unknown	RT	NR	Not relevant	62 (AWD)
8/M/75	Solitary tumor on left upper arm area	Unknown	Excision	CR	Skin	18 (AND)
9/M/60	Solitary tumor on forehead	Unknown	Excision	CR	No	13 (AND)
10/M/41	Solitary tumor on upper part of left leg	48	RT	CR	No	90 (AND)
11/M/74	Solitary nodule on back	12	RT	CR	No	12 (AND)
12/M/53	Localized nodules on scalp	2	RT	CR	No	23 (AND)
13/M/42	Solitary tumor on left upper arm area	48	RT	CR	No	32 (AND)
14/F/52	Solitary nodule on left upper arm area	24	RT	CR	No	66 (AND)
15/M/28	Multiple plaques on both legs	96	Wait and see	NR	Not relevant	61 (AND)
16/F/42	Multiple plaques on both arms and shoulders	60	Wait and see	NR	Not relevant	127 (AWD)
17/F/63	Multiple papules on abdomen	48	Wait and see	PR	Not relevant	38 (AWD)
18/M/78	2 Plaques on both flanks	6	Wait and see	CR	No	13 (DOC)
19/F/74	3 Nodules and 1 plaque on right leg	6	Topical steroids	CR	Skin	17 (AND)
20/M/62	Multiple papules on right shoulder and abdomen	6	Topical steroids	CR	No	17 (AND)
21/M/47	2 Plaques on lower part of both legs	24	Topical steroids	CR	No	12 (AND)
22/F/54	2 Nodules on back and left shoulder	6	Excision	CR	Skin	17 (AND)
23/F/48	3 Nodules on left arm and abdomen	4	Excision	CR	Skin	48 (AND)
24/M/25	Nodules on upper part of both arms and back	6	RT	CR	Skin	35 (AND)
25/F/38	3 Plaques on right lower arm area and left upper arm area	24	RT	CR	Skin	115 (AND)
26/F/74	3 Tumors on forehead and cheeks	120	RT	CR	Skin	31 (AWD)
27/M/35	Plaques on back, upper part of arms, and upper part of right leg	48	RT	CR	Skin	76 (AND)
28/M/70	Tumor and plaques on back	12	RT	CR	No	38 (AND)
29/M/34	Plaques on the upper and lower parts of back	60	RT	CR	Skin	33 (AND)
30/M/65	Plaques and nodules on face	6	RT	CR	Skin	36 (AND)
31/M/30	2 Tumors on back and right hip	4	RT	CR	Skin	30 (AND)
32/M/33	Nodule on right upper arm area and plaque on back	36	RT	CR	Skin	97 (AND)
33/M/21	4 Nodules on upper and lower back areas	21	RT	CR	Skin	18 (AND)
34/F/65	Tumor and plaques on lower part of right leg	6	RT	CR	No	109 (AND)
35/M/30	Tumors on back and upper part of right leg	180	Chlorambucil	PR	Not relevant	186 (AND)
36/M/48	Multiple tumors on both legs	48	Chlorambucil	CR	No	120 (AND)
37/M/52	Multiple papules and nodules on trunk and legs	9	Chlorambucil	PR	Not relevant	26 (AND)
38/F/73	Multiple plaques and tumors on back, buttocks, and upper part of legs	2	Chlorambucil	CR	No	26 (AND)
39/M/41	2 Plaques on upper and lower parts of back	2	Chlorambucil	CR	No	15 (AND)
40/M/44	Multiple nodules and tumors on trunk and extremities	7	Chlorambucil	PR	Not relevant	27 (AWD)
41/M/32	Multiple nodules on back and in right knee cavity	24	Chlorambucil	PR	Not relevant	16 (AWD)
42/M/46	2 Plaques on lower part of both legs	60	Chlorambucil	CR	No	32 (AND)
43/M/36	Multiple nodules on back	12	Chlorambucil	CR	Skin	33 (AND)
44/F/69	Multiple nodules on back	24	Chlorambucil	CR	No	37 (AND)
45/M/71	Multiple nodules on chest, cheeks, and back	8	Chlorambucil	PR	Not relevant	59 (AWD)
46/M/46	Multiple nodules on both arms and legs	48	CT	CR	Skin	16 (AND)
47/M/52	Multiple nodules on back and upper part of arms	12	CT	CR	Skin	41 (AWD)
48/F/60	Multiple plaques on trunk and arms	24	CT	CR	EC	96 (AWD)
49/F/53	Multiple nodules on trunk and legs	60	CT	CR	Skin	121 (AWD)
50/F/62	Multiple tumors and plaques on trunk and extremities	10	CT	PR	Not relevant	33 (AWD)

Abbreviations: AND, alive with no evidence of disease; AWD, alive with disease; CR, complete remission; CT, multiagent chemotherapy; DOC, died of other cause; EC, extracutaneous relapse; NR, no response; PR, partial remission; RT, radiotherapy.

Cutaneous relapses were treated variously with topical or intralesional steroids, surgical excision, radiotherapy, chlorambucil, or interferon alfa. Local radiotherapy was administered to 4 patients at a dose of 2×200 rads (2 Gy), resulting in a complete remission in 1 patient and a partial remission in the other 3 patients. A "wait-and-see" policy was followed, particularly in patients with multiple skin relapses.

Development of extracutaneous disease occurred in only 2 of 50 patients. A 52-year-old man (patient 37) who presented with multiple nodules on his back, chest, and both legs was treated with 6 mg/d of chlorambucil for

Table 2. Summary of Main Clinical Characteristics in 50 Cases of Primary Cutaneous Marginal Zone B-Cell Lymphoma

Clinical Characteristics	No.
Age at diagnosis, median (range), y	50 (21-78)
Sex, M/F	35/15
Duration of skin lesions before diagnosis, median (range), mo	12 (1-180)
Morphological type of skin lesions*	
Papules	3
Plaques	17
Nodules	21
Tumors	18
Extent of skin lesions	
Solitary	11
Localized	3
Multifocal	36
Localization of skin lesions	
Head and neck	6
Trunk (total)	30
Arms	17
Legs	17
Results of initial treatment	
Complete remission	40
Partial remission	7
No response	3
Progressive disease	0
Relapse	
Skin	19
Extracutaneous	1
Skin and extracutaneous	0
Duration of follow-up after diagnosis, median (range), mo	36 (12-186)
Current status	
Alive without disease	36
Alive with disease	13
Died of lymphoma	0
Died of unrelated cause	1

*In 8 patients, a combination of different types of skin lesions were present.

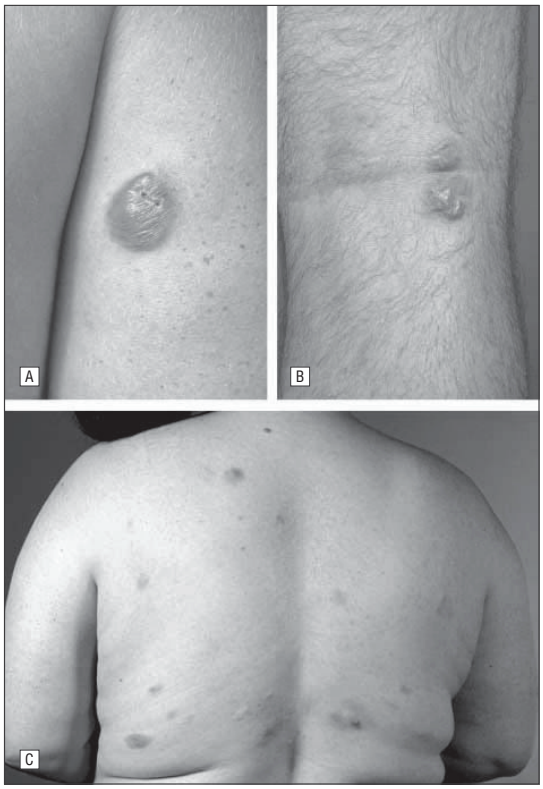

Figure 1. Primary cutaneous marginal zone B-cell lymphoma (PCMZL). A, A patient with PCMZL who presented with a solitary nodule on the right upper arm area. B, A patient with PCMZL who presented with localized nodules in the knee cavity. C, A patient with PCMZL who presented with multifocal skin lesions on her back and the lower part of her arms.

23 weeks, resulting in a partial remission of his skin lesions. Nodal involvement and progression of skin lesions developed 1 month after his treatment with chlorambucil was discontinued. Histologic examination at the time of disease progression showed blastic transformation of the tumor cells in the skin and lymph node biopsy specimens. Subsequent courses of chemotherapy—including CHOP; dexamethasone, cytarabine, and cisplatin (DHAP); and doxorubicin, cyclophosphamide, vincristine, methotrexate, bleomycin, and prednisone (MACOP-B)—ultimately resulted in complete remission of the nodal localizations. Skin localizations are continuously present and are treated with local radiotherapy on clinical demand.

A 60-year-old woman (patient 48) developed histopathologically proved involvement of cervical lymph nodes without concurrent skin localizations 2 years after diagnosis. Because the enlarged lymph nodes regressed spontaneously, no treatment was initiated. During the next 6 years, several relapses of lymphadenopathy occurred, each of which was followed by complete spontaneous regression.

After a median follow-up of 36 months (mean, 52 months; range, 12-186 months), 49 patients were alive: 36 were in complete remission and 13 had ongoing disease. One patient died of unrelated disease, but no patients died of lymphoma.

COMMENT

In the present study, we reviewed the clinical and therapeutic features in 50 cases of well-defined PCMZL. The majority of the patients (36 [72%]) presented with multifocal skin lesions, while a much smaller percentage (14 [28%]) had solitary or localized disease at presentation. The skin lesions were localized preferentially on the trunk and extremities and, unlike primary cutaneous follicle center lymphomas, uncommonly in the head and neck region. The results of this retrospective study confirm the indolent clinical behavior and excellent prognosis in these cases of PCMZL. After a median follow-up of 36 months, only 2 (4%) of 50 patients had developed extracutaneous disease, and none of the 50 patients had died of lymphoma, which is in accordance with previous studies.[7-10] However, skin relapses are common in this type of cutaneous B-cell lymphoma and were observed in 19 (48%) of 40 patients. The estimated 5-year relapse-free

Table 3. Initial Treatment, Therapeutic Effects, and Data on Relapse of Disease in 50 Cases of Primary Cutaneous Marginal Zone B-Cell Lymphoma (PCMZL)

Therapy	Total No. of Patients	CR	PR	No Response	Progression of Disease	Cutaneous Relapse After CR	Extracutaneous Relapse After CR
Patients With PCMZL and Solitary or Localized Skin Lesions (n = 14)							
Excision	8	8	0	0	0	3	0
Radiotherapy	6	5	0	1	0	0	0
Patients With PCMZL and Multifocal Skin Lesions (n = 36)							
Wait and see	4	1*	1	2	0	0	0
Topical steroids	3	3	0	0	0	1	0
Excision	2	2	0	0	0	2	0
Radiotherapy	11	11	0	0	0	9	0
Chlorambucil (Leukeran)	11	6	5	0	0	1	0
Multiagent chemotherapy	5	4	1	0	0	3	1

Abbreviations: CR, complete remission; PR, partial remission.
*One patient showed a complete spontaneous remission of skin lesions.

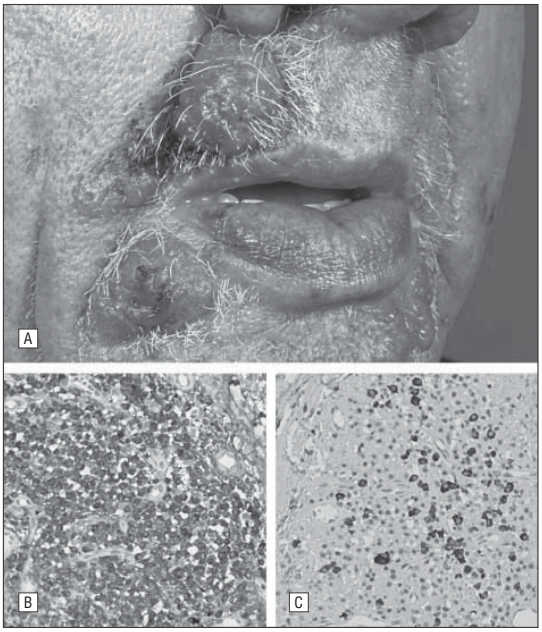

Figure 2. Primary cutaneous marginal zone B-cell lymphoma (PCMZL). A, A patient with PCMZL who presented with perioral tumors. B and C, Histopathologic examination shows a dermal infiltrate with an almost pure population of plasma cells. The plasma cells show cytoplasmatic expression of λ immunoglobulin light chain (B) but are negative for κ light chain (C).

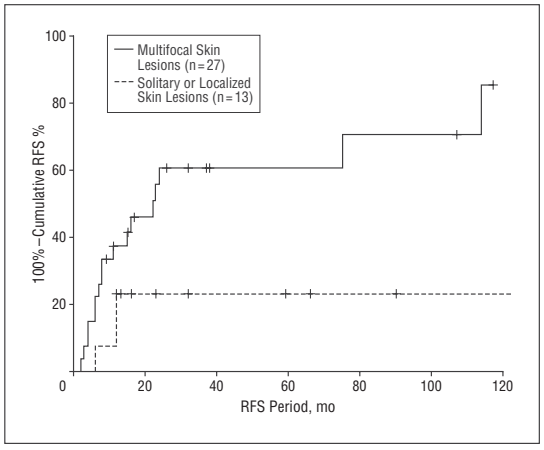

Figure 3. Relapse-free survival (RFS) in 27 patients with primary cutaneous marginal zone B-cell lymphoma (PCMZL) who presented with multifocal skin lesions (5-year RFS rate, 39%) and in 13 patients with PCMZL who presented with solitary or localized skin lesions (5-year RFS rate, 77%).

survival rate after complete remission was 51%, which is significantly lower than that for patients with primary cutaneous follicle center lymphomas (72%; N.J. Senff, MD, J.J.H., M.H.V, and R.W., unpublished data, ongoing study). Skin relapses were much more common in patients who presented with multifocal skin lesions (5-year relapse-free survival rate, 39%) than in patients who presented with solitary or localized skin lesions (5-year relapse-free survival rate, 77%).

One of the goals of our study was to evaluate our current therapeutic approach for PCMZLs. In general, a distinction is made between the treatment of initial skin lesions and the treatment of relapsing disease. A wait-and-see strategy is often followed, with palliative treatment of larger or disturbing skin lesions, particulary in patients with frequently relapsing skin lesions.

With respect to initial treatment, patients who presented with solitary or localized skin lesions were treated with either local radiotherapy or surgical excision, resulting in complete remission in 13 of 14 patients; skin relapses were observed in only 3 of the 13 patients. The optimal dose of radiotherapy is unknown. Whereas a dose of 4000 rads (40 Gy) was previously used in patients who presented with solitary lesions, treatment with 3000 rads (30 Gy) has recently proved equally effective. Radiotherapy was ineffective in 1 patient who presented with slowly progressive perioral skin tumors that were histologically characterized by an almost pure population of IgG-λ–positive plasma cells. A similar experience with another patient, who presented with a solitary tumor on the face, with a pure population of monotypic plasma cells (not included in

this study), suggests that local radiotherapy should not be used in such cases.

The optimal treatment of patients who present with multifocal skin lesions is less obvious, as illustrated by the large variety of therapies used in the present series. In cases with only a few scattered skin lesions, low-dose radiotherapy (2000 rads [20 Gy]) was often used. All 11 patients treated in this way reached complete remission, but skin relapses were observed in 9 of 11 cases, indicating that this approach provides excellent palliation but has low curative potential.

Another 11 patients, who generally presented with more extensive skin disease, were treated with chlorambucil for periods varying between 8 and 23 weeks. For many years, chlorambucil has been used as an effective treatment option in chronic lymphocytic leukemia and low-grade non-Hodgkin lymphomas, including lymphomas of mucosa-associated lymphoid tissue.[15-18] Apart from a single case report, therapeutic experience with chlorambucil therapy for PCMZL has not previously been published.[19] In 6 (55%) of 11 patients, a complete remission was achieved in a median treatment period of 13 weeks, and only 1 of the 6 patients has since developed a local recurrence of disease. In another 4 patients, a partial remission was observed. The results of the present study indicate that chlorambucil therapy is effective and safe for the treatment of patients who have PCMZL with multifocal skin lesions.

More extensive chemotherapy, including COP or CHOP, was administered to 5 patients, 4 of whom achieved complete remission. However, relapses were observed in all of them, indicating that multiagent chemotherapy is not an attractive mode of treatment in patients with PCMZL.

Evaluation of the results of the present study suggests that new patients who present with solitary or localized skin lesions can be treated effectively with a 3000-rad (30-Gy) dose of radiotherapy or with surgical excision, which will often result in sustained complete remissions. Also, in patients with multifocal skin lesions at first presentation, attempts should be made to obtain a durable complete remission. In the present study, treatment with chlorambucil resulted in sustained complete remissions in approximately 50% of patients who presented with extensive skin lesions. In patients who presented with only 2 or 3 scattered skin lesions, radiotherapy (2000 rads [20 Gy]) or surgical excision of the individual skin lesions may be attempted first. Recent studies also report beneficial effects from the intralesional or subcutaneous administration of interferon alfa and of rituximab (anti-CD20 monoclonal antibody) in patients with PCMZL.[20-23] However, prospective multicenter studies are necessary to evaluate the long-term efficacy of these new therapies compared with the traditional therapies described herein.

In patients who develop chronically relapsing disease, treatment is aimed at palliation rather than sustained complete remission, and the benefits of treatment should be weighed carefully against their potential adverse effects. In such patients, an expectant strategy, similar to that used in other indolent B-cell lymphomas and leukemias, should be considered. Individual skin lesions can be treated with topical or intralesional steroids or low-dose radiotherapy, if required.

Finally, recent studies showed an association between *B burgdorferi* infection and a significant minority of PCMZL cases in endemic areas in Europe.[24,25] In contrast, such an association was not found in American and Asian cases.[26,27] Analogously, a strong association has been found between *Helicobacter pylori* infection and gastric marginal zone lymphoma. This observation has had major therapeutic implications. Many early cases of gastric marginal zone lymphoma can now be treated solely and effectively by the eradication of *H pylori* infection with antibiotic therapy. Based on some anecdotal reports on the disappearance of *B burgdorferi*–associated PCMZL after antibiotic treatment (penicillin, cephalosporins, or tetracyclines), recent reviews and textbooks suggest that such cases should be treated with antibiotics first, before other treatments are used.[9,20,28,29] However, other reports did not confirm the favorable results of antibiotic treatment in cases of PCMZL.[30,31] The present study included 5 patients who had a positive *Borrelia* serologic test result, which was not further confirmed by culture or polymerase chain reaction analysis. None of these patients responded to doxycycline therapy (200 mg/d for 1 month). Additional studies are therefore required to establish which patients may benefit from antibiotic treatment and to assess which type, dose, and duration of antibiotic treatment are most efficacious.

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