CASE REPORT

Durable Regression of Primary Cutaneous B-Cell Lymphoma Following Fever-inducing Mistletoe Treatment: Two Case Reports

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Conflict of Interest
The authors declare no competing interests.

ABSTRACT

Background: Mistletoe is a complementary cancer treatment that is widely used, usually in addition to and alongside recommended conventional cancer therapy. However, little is known about its use, effectiveness, and safety in the treatment of cutaneous lymphoma.

Case Report: Two patients with primary cutaneous B-cell lymphoma ($pT_{2b}cN_xM_o$ follicle center and $pT_{2a}cN_xM_o$ marginal zone) either declined or postponed recommended conventional treatment and received high-dose, fever-inducing mistletoe treatment; a combination of intratumoral, subcutaneous, and intravenous application was given; and one patient also underwent whole-body hyperthermia. The lymphoma regressed over a period of 12 and 8 months, respectively, and after administration of a cumulative dose of 12.98 g and 4.63 g mistletoe extract, respectively. The patients are in remission to date, 3.5 years after commencement of treatment. Neither patient received conventional cancer treatment during the entire observation period.

摘要

背景：槲寄生疗法是一种广泛使用的补充性癌症治疗方法，通常作为常规癌症治疗的补充疗法，或伴随常规疗法共同使用。然而，在皮肤淋巴瘤的治疗过程中，人们对该疗法的使用、有效性和安全性知之甚少。

病例报告：两名原发性皮肤B-细胞淋巴瘤患者（pT2bcNxM0滤泡中心和pT2acNxM0边缘区域）取消或推迟推荐的常规治疗，并接受高剂量、可引起发热的槲寄生疗法；通过瘤内、皮下和静脉注射方式进行组合给药，其中一名患者还接受了全身过热疗法。这两名患者在分别接受12.98g和4.63g累积剂量的槲寄生提取物治疗后，分别在12个月和8个月后淋巴瘤出现退化。迄今为止，即在开始治疗的3年半之后，患者病情正处于缓解期。在整个观察期期间，两名患者都未接受常规癌症治疗。

RESUMEN

Antecedentes: El muérdago es una planta que se utiliza ampliamente como tratamiento oncológico complementario, por lo general, en forma concomitante con la terapia convencional recomendada. Sin embargo, no se sabe mucho sobre su uso, efectividad y seguridad en el tratamiento del linfoma cutáneo.

Caso clínico: Dos pacientes diagnosticados con linfoma cutáneo primario de células B (centro folicular pT2bcNxMo y zona marginal pT2acNxMo) habían rechazado o pospuesto el tratamiento convencional recomendado para estos casos, y recibieron dosis altas de tratamiento con muérdago, que provoca fiebre. Se administró una combinación de inyección intratumoral, subcutánea e intravenosa (IV), y uno de los pacientes también sufrió hipertermia en todo el cuerpo. Se registró un retroceso del linfoma en un período de 12 y 8 meses, respectivamente. Esto sucedió luego de que se administrara una dosis acumulativa de 12,98 g y 4,63 g de extracto de muérdago, respectivamente. A la fecha, los pacientes se encuentran en etapa de remisión, luego de transcurridos 3 años y medio desde el inicio del tratamiento. Ninguno de ellos recibió tratamiento oncológico convencional durante todo el período de observación.

Long-term remissions of lymphoma after fever-inducing therapy with bacterial toxins have been documented since William Coley.[1] Primary cutaneous lymphomas make up about 5% of all non-Hodgkin's lymphoma (annual incidence, 1:100000); 20% to 25% of these are primary cutaneous B-cell lymphomas (PCBCL).[2-4] The most common subtypes are primary cutaneous follicle center lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL), and diffuse large cell lymphoma. The follicle center and marginal zone B-cell lymphomas tend to be indolent and have a 5-year survival of more than 95%[5]; although relapses are common, systemic progression is rare. Single lesions are treated with radiotherapy, intralesional steroids, surgical excision, or a "wait and see" strategy. Multifocal or relapsed systemic disease is usually treated with rituximab (R, anti-CD20 monoclonal antibody), single- or multi-agent chemotherapy (eg, chlorambucil or cyclophosphamide; vincristine; prednisolone; cyclophosphamide, vincristine, and predisolone [CVP]), or

immunotherapy with interferon-α.[6, 7] PCBCL is associated with immune dysregulation and in some instances immunodeficiency with chronic inflammation (particularly PCMZL), eg, in rheumatoid arthritis or Sjögren's syndrome and with *Borrelia burgdorferi* infection.[8-12] They respond to immunological treatments like intralesional injections of interferon-α[13] or adenovirus-encoding interferon-γ, which can even lead to remission in non-injected distant lesions.[14] Survival in systemic lymphoma correlates with tumor-infiltrating immune cells,[15] and for the occasionally observed spontaneous regressions of non-Hodgkin's lymphoma, immunologic mechanisms have been proposed.[16,17]

Mistletoe extract (ME) is a whole plant remedy derived from *Viscum album* L, a hemi-parasitic shrub; it is widely used for complementary cancer treatment, especially in Europe, in conjunction with conventional therapy.[18] A variety of biologically active compounds have been isolated from ME, including mistletoe lectins (MLs), viscotoxins, oligo- and polysaccharides, and others.[19,20] ME has immunostimulatory activity (in vivo and in vitro activation of monocytes/macrophages, granulocytes, natural killer cells, T-cells, dendritic cells, induction of a variety of cytokines[19,20]), and several compounds (ML in particular) are cytotoxic with established apoptosis-inducing effects.[19-21]

ME is usually applied subcutaneously at a low starting dose, which is slowly titrated upwards and adjusted individually. This approach is associated with improvement of quality of life and probably also survival.[22-24] Tumor remission has rarely been observed with low dosages, but mainly after high, fever-inducing ME dosage, often injected intratumorally or as an intravenous (IV) infusion.[22-24] However, these observations have been reported only in case series and case reports.[23-27] No randomized trials have yet investigated the role of ME in the treatment of lymphoma. Apart from dose-dependent flu-like symptoms, fever, and inflammatory reactions at the injected sites, ME treatment is safe. Occasionally, hypersensitivity reactions are reported.[28]

Two patients with primary cutaneous lymphoma were treated at the Park Attwood Clinic (PAC, which closed in 2010), a British center specializing in complementary cancer care and particularly in high-dose and fever-inducing ME treatment. Informed consent for ME treatment was obtained from both patients with the understanding that this would not replace recommended therapies and there was good evidence that ME could improve tolerance of mainstream treatment when applied concurrently.

CASE 1: PRIMARY CUTANEOUS FOLLICLE CENTER B-CELL LYMPHOMA

A 51-year-old female presented with 2 lesions on the left lower leg in May 2008 at the oncology department of a large tertiary hospital (Aberdeen Royal Infirmary [ARI]). She had first noticed in the summer of 2007 a lesion in the left upper Achilles region, which increased in size and became red. In autumn 2007, a similar lesion developed over the mid shin of the same leg, and in the weeks leading up to presentation, a couple of much smaller satellite lesions appeared around the anterior lesion.

Histopathology confirmed grade 1 follicular B-cell lymphoma (Figures 1 and 2). Staging computed tomography (CT) scan (chest, abdomen, pelvis) reported no intraabdominal or pelvic lymphadenopathy but showed one 2.7 x 1.7 inguinal lymph node, which was not biopsied. Stage was $pT_{2b}cN_xM_{0.}$[26] Hematology, biochemistry, and trephine bone marrow biopsy were essentially normal. IgH gene rearrangement analysis found clonality, confirming B-cell lymphoma; T-cell receptor (TCR)-β–ve; TCR-γ very weakly polyclonal. Cytogenetics: t(11;14) and t(14;18) translocations were not tested.

The patient was generally well; she had no history of injury or infection and no B symptoms, such as fatigue, night sweats, weight loss, or pruritus. She had longstanding assumptive skin lipomas in different areas of the body but had been generally healthy, had a grown daughter, worked as a movement therapist, was a non-smoker, drank no alcohol, took no regular medications, and reported no allergies.

In view of the multicentric lesions, with satellites and possible regional node involvement indicative of advancement, it was recommended she undergo systemic immuno-chemotherapy with 6 cycles of cyclophosphamide,

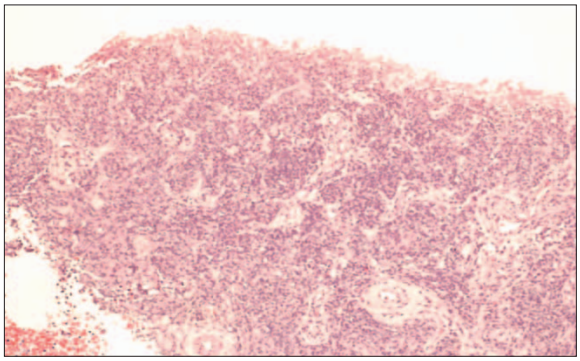

Figure 1 Cellular lymphoid tumor. The pattern is largely diffuse with focal nodular areas (H&E x10). *Image courtesy of Dr Ghada Bashat, Pathology, Aberdeen Royal Infirmary.*

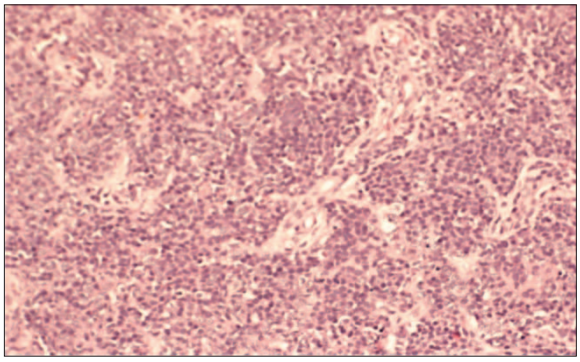

Figure 2 Cellular lymphoid tumor. The pattern is largely diffuse with focal nodular areas (H&E x20). *Image courtesy of Dr Ghada Bashat, Pathology, Aberdeen Royal Infirmary.*

vincristine, and prednisone plus rituximab (R-CVP) and involved-field radiotherapy on completion of the cycles. Although the patient was not opposed to this treatment in principle, she decided to keep it in reserve and improve her immunity with ME treatment first.

On presentation for ME treatment in June 2008, the patient had a posterior lesion in the left proximal Achilles region measuring 5 cm x 4 cm (Figure 3) and an anterior mid shin tumor measuring 4 cm x 2 cm (Figure 4), with a number of surrounding satellites, each < 1.5 cm. The 2 large lesions were raised, red, and warm to the touch. The overlying skin was thinned but intact. There were no signs of deep tissue infiltration; she reported no pain, and no neurological deficits were ascertained. The left leg was well perfused, but there was pitting edema around the lesions and the ankle.

Treatment

Treatment with ME (using *Abnobaviscum fraxini*) comprised a combination of IV, intratumoral (IT), and subcutaneous (SC) applications over 12.3 months and IV and SC application over another 8 months. Details are shown in Table 1. Treatment was subdivided in an induction phase, wherein febrile reactions to ME are elicited, and a postinduction phase. ME treatment was combined with whole-body hyperthermia (WBHT)—a technique to increase core temperature to 39˚ to 39.5˚C for 2 to 5 hours with water-filtered infrared A radiation

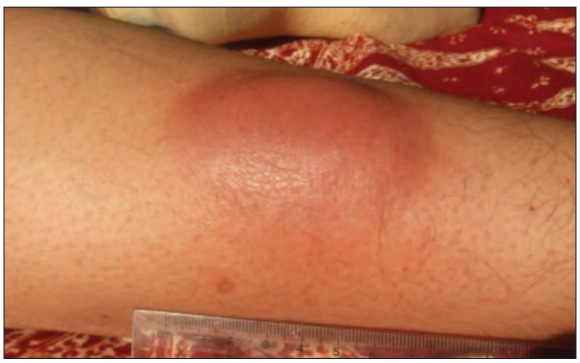

Figure 3 Primary cutaneous B-cell lymphoma in July 2008. Posterior lesion left lower leg.

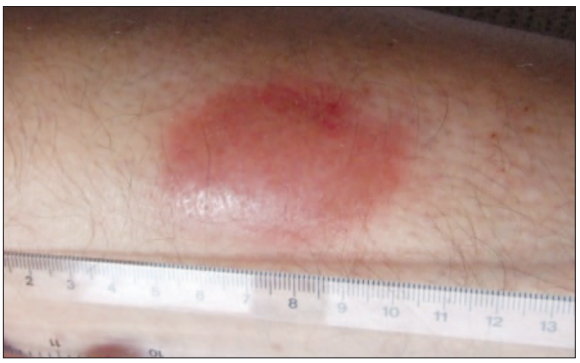

Figure 4 Primary cutaneous B-cell lymphoma in July 2008. Anterior lesion left lower leg; surrounding satellites not showing clearly.

Table 1 Treatment Schedule (06/02/08-06/08/09) of Patient With PCBCL[a]

Month	Day or Interval	ME Dosage (mg) Per Application: IV Treatment[b]	IT Treatment	SC Treatment (no. of sessions, if > 1)	WBHT
		Induction phase			
0	1	40	—	—	
	2	80	—	1	
	3	160	1	10	
	4	—	4	20	
	8	160	10	30	
	11	160	20	20	
	15	160	—	40	
		Post-induction phase			
	16	—	40	40	
	18	160	—	—	
	21-28[c]	—	—	(3 x) 40	
	25	200	—	—	
1	29-35	—	—	(2 x) 40	
	32	200	—	—	
	36-42	—	—	40	
	36	200	80	—	
	37	—	40	—	No. 1
	42	200	120	—	No. 2
	43-49	—	—	(2 x) 40	
	46	200	—	—	
	50-56	—	—	(2 x) 40	
	53	200	—	80	
2	57	—	240[d]	—	
	58	200	—	—	No. 3
	61	—	—	—	
	64-70	—	—	(2 x) 40	
	67	200	320[d]	—	
	71-77	—	—	(2 x) 40	
	74	200	—	—	
	78	—	320[d]	40	
	79	200	—	—	No. 4
3	85-91	—	—	40	
	88	200	320[d]	—	
	92-98	—	—	(2 x) 40	
	95	200	—	—	
	99	—	320[d]	—	
	100	200	—	—	No. 5
	103-112	—	—	(2 x) 40	
	109	200	—	—	
	113-119	—	—	(2 x) 40	
	116	200	—	—	
4	120	—	320[d]	20	
	127-140	—	—	(4 x) 40	
	135	200	—	—	No. 7
5	141-161	—	—	(5 x) 40	
	162	—	360[d]	—	
	163	200	—	—	No. 8
6	169-182	—	—	(3 x) 40	
	178	200	—	—	
	183-189	—	—	(2 x) 40	
	190	—	400[d]	—	
	191	200	—	—	No. 9
	197-210	—	—	(4 x) 40	
	204	200	—	—	
	211-231	—	—	(6 x) 40	
	233	—	400[d]	—	
	234	200	—	—	No. 10
	237-271	—	—	(12 x) 20	
	254	200	—	—	
	272	—	400[d]	—	
	279-369	—	—	(13 x) 40	
	338	200	—	—	
12	370	—	240[d]	—	
	371	200	—	—	No. 12
	372	End of IT treatment; subsequent IV and SC treatment and WBHT not shown.			
Total					
No. of applications		33	19	81	12 x
ME dosage		6120	3950	2901	

Abbreviations: IT, intratumoral; IV, intravenous; ME, mistletoe extract; PCBCL, primary cutaneous B-cell lymphoma; SC, subcutaneous; WBHT, whole-body hyperthermia.

[a] Month and day (interval) of treatment; mode, dose, and number of ME applications; application of WBHT.

[b] Infused in 250 mL sodium chloride 0.9%, over 60-90 minutes.

[c] Treatment periods of 1 or more weeks during which SC injections were given.

[d] IT distributed over both lesions.

under controlled conditions. The skin lesions were not directly targeted. She had no other cancer treatments and was not taking any medications.

During induction, the patient had 4 febrile responses of ≥38.5˚C lasting < 24 hours with maximum readings of 38.5˚C (after day 3); 38.7˚C (after day 4); 39.1˚C (after day 8); and 38.6˚C (after day 11). For the IT approach, the lesions were injected from the healthy skin margins to avoid breaking the paper-thin skin overlying the bulging tumors. The volume of ME fluid often exceeded 20 mL (20 mg/mL/ampoule) and was injected evenly intra- and perilesional while repositioning the needle during injection.

After IT treatment, the lesions responded with immediate postinjection swelling and inflammation, followed by clinical resolution of inflammation, and over the course of treatment, the lesions successively appeared less inflamed. The rate of regression seemed slightly accelerated after starting WBHT (day 37), and after 4 months, there was a clear overall improvement. The lesions continued to show injection-associated fluctuations, and the posterior lesion resolved first.

The lesions steadily decreased in volume, consistency, and redness. The remission was assessed by visual inspection and palpation and confirmed by 3 independent clinicians from 3 different clinical settings, including the ARI. The overall fitness and stamina of the patient improved. Re-scanning in May 2009 reflected "No significant supraclavicular, axillary or mediastinal . . . retroperitoneal or pelvic lymphadenopathy; as before, there are inguinal nodes the largest of which is on the left and measuring 1.3 x 1.8 cm. This node was documented as 2.7 x 1.7 cm on staging." Routine full blood count and biochemistry were normal. Given the favorable clinical signs of control, the IT injections were discontinued at 12.3 months. Combined IV and SC ME treatment with WBHT continued for another 8 months, and the lesions continued to regress. The areas blanched eventually, leaving depressed (posterior, Figure 5) and level (anterior lesion, Figure 6) hyperpigmented areas. Conventional therapy was deferred indefinitely. At last review in December 2011, the patient was doing well and remained in remission; the appearances were similar to those from June 2011 (Figures 7 and 8).

Tolerability

Fever was associated with sickness (grade 1) and grade 2 to 3 fatigue. The subsequent combined IV/IT administrations elicited fatigue (grade 1-2) for 1 to 3 days. No hypersensitivity was observed. SC injections elicited site responses of 4 cm to 5 cm erythema for < 2 days. The intralesional injections with concentrated ME were uncomfortable, with fluid pressure and pain for a few minutes, but did not require analgesia. Inflammatory responses (erythema, swelling, tenderness) and (transient) increase of edema of the lower leg lasted for < 2 days and were treated with cooling applications. The patient had no phlebitis at cannulation sites.

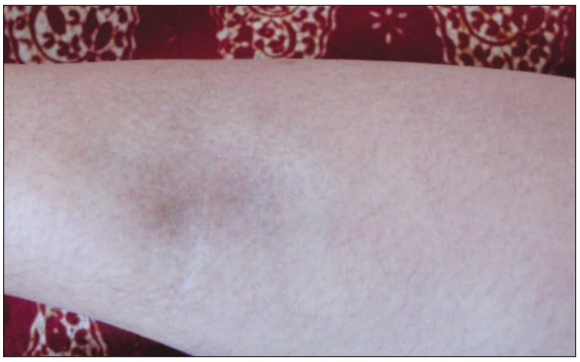

Figure 5 Primary cutaneous B-cell lymphoma in May 2010. Posterior left lower leg; posttreatment pigmentation and depression.

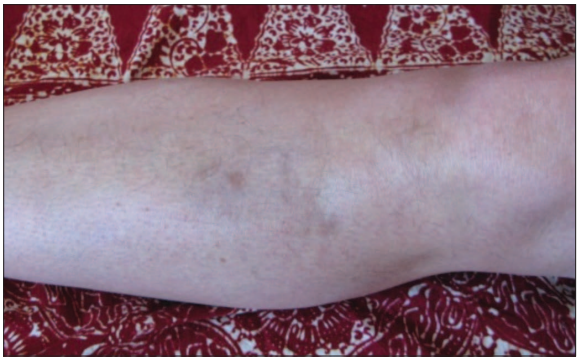

Figure 6 Primary cutaneous B-cell lymphoma in May 2010. Anterior left lower leg showing pigmentation changes.

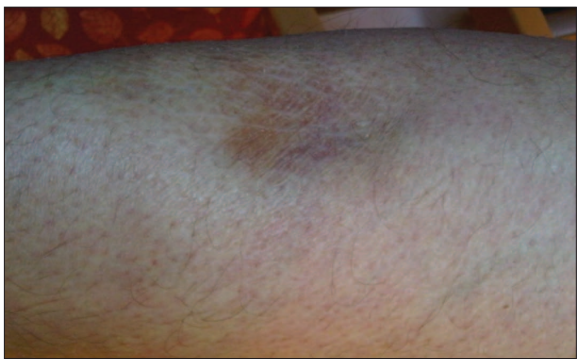

Figure 7 Primary cutaneous B-cell lymphoma in June 2011. Posterior left lower leg.

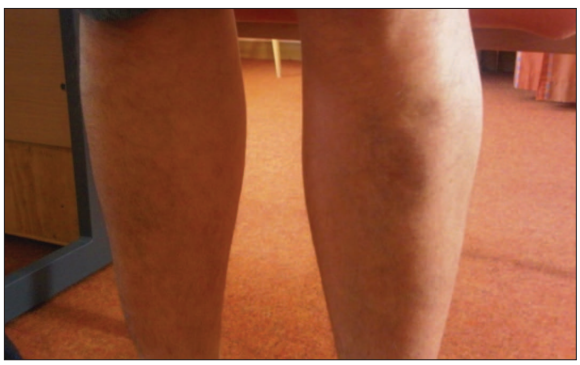

Figure 8 Primary cutaneous B-cell lymphoma in June 2011. Anterior left lower leg.

Patient's Description of Treatment

The patient in this case described the treatment experience as follows:

> *With the initial fevers and fluctuating energy levels, my treatment was intense, exhausting and it was the only thing I could do during that time: but not a burden and a meaningful experience. During one of the high fevers an old traumatic experience became disentangled and I have felt freed up since; I now feel better than before my cancer, physically and emotionally. I also felt empowered by the working together with my doctors to develop the best treatment for me. I am very grateful for my new health!*

CASE 2: PRIMARY CUTANEOUS MARGINAL ZONE B-CELL LYMPHOMA

A 52-year-old flight attendant was diagnosed at the same oncology department (ARI) with stage 2A, $pT_{2a}cN_xM_0$ primary cutaneous marginal zone B-cell lymphoma (PCMZL). In December 2007, 2 to 3 days after venapunction, he developed a lesion in the left antecubital fossa, which was excised in May 2008. The histopathology showed nodal marginal zone lymphoma (Figure 9). A staging CT scan of the neck, chest, abdomen, and pelvis showed no signs of systemic disease; trephine bone marrow biopsy, biochemistry, and hematology were normal. Shortly after excision, the patient developed a second lesion on the right anterior chest wall, medial to the right anterior axillary fold. The lesion was only palpable (no photographs). The patient was asymptomatic, had no recent weight loss or fatigue. Several treatment options were recommended: R-CVP, 10 fractions of involved-field radiotherapy of the 2 sites, or 6 months' pulsed chlorambucil; he declined these options.

The patient had a history of rosacea with keratitis; actinic keratoses of upper back (treated with occasional cryotherapy); 2 basal cell carcinomas—one of the upper back (excised 1999) and one of the left leg (excised early 2007)—and an uncertain diagnosis of facial cutaneous scleroderma with no visceral involvement, but raised titres of antinuclear factor, which was unresponsive to azathioprine and oral prednisolone (2004). He used nicotine and alcohol moderately. Apart from emollients, he used no other regular conventional medications, reported no formal allergies, and was mistletoe-naïve. He had had no recent infections and no soft tissue trauma.

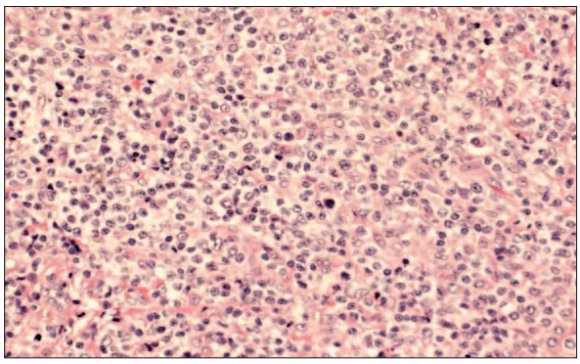

Figure 9 Nodular marginal zone lymphoma. The architecture of the node is diffusely effaced by a population of lymphoid, plasmacytic, and histiocytic cells (H&E x10). *Image courtesy of Dr Ghada Bashat, Pathology, Aberdeen Royal Infirmary.*

On presentation at PAC in August 2008, the patient was in good general health, with a Karnofsky Performance Scale status of › 90%. There was one soft and mobile lymph node in the left axilla. The right upper thoracic lesion was 2 x 3 cm palpable and mobile. There were no other abnormal findings.

Treatment

Combined IV, IT, and SC treatment with ME (*Abnobaviscum fraxini*) was provided over a period of 8.5 months. Details are shown in Table 2. During informed consent, it was explained to the patient that his underlying autoimmune condition theoretically could be aggravated. He received no other anticancer treatments.

He had 6 febrile responses (38˚ to 39.2˚C) between days 5 and 87. There were no signs of concomitant infection. After IT injections, the lymphoma lesion each time showed a similar response pattern of inflammatory swelling and erythema for up to 2 days, then resolution. The lesion increased in size over the first month to 4 x 5 cm, then remained unchanged for 3 months, and after the IT dose was increased to 100 mg ME, the lesion steadily diminished to become impalpable at 8.5 months (Table 2). This complete response (CR) was clinically verified by 3 clinicians in 2 separate institutions, including the ARI. The ITs were ceased in April 2009, and SC and IV treatment was continued until November 2010. A CT scan in March 2010 was unremarkable. The patient was last reviewed in December 2011 and was doing well and in remission; no new lesions had developed.

Tolerability

During the first 3 months, treatment was challenging. The fever episodes in particular were accompanied by sickness and grade 1 to 2 fatigue. Once, grade 2 phlebitis developed at an IV cannulation site and resolved spontaneously; interestingly, no local relapse resulted from this. The SC and IT doses were followed by typical inflammatory site reactions that resolved without scarring or subcutaneous fibrosis. No hypersensitivity and no signs or symptoms of autoimmune reactivation were observed. After 6 months, the patient consistently reported improved vitality and well-being.

Patient's Description of Treatment

The patient in this case described the treatment experience as follows:

> *When I was offered chemo-/radiotherapy, this seemed aggressive to me like a sledge hammer* [sic] *to crack a nut. My understanding of mistletoe ther-*

Table 2 Treatment Schedule (08/09/08-04/20/09) and Tumor Size of Patient With PCMZL[a]

Month	Day or Interval	ME Dosage (mg) Per Application: IV Treatment[b]	IT Treatment	SC Treatment (no. of sessions, if > 1)	Tumor Size (cm) Palpation
		Induction phase			
0	1	40	—	—	3 x 2
	2	80	—	0.2	
	3	160	—	—	
	4	200	2	0.2	
	5	—	10	—	
	7	200	20	—	
	10	200	40	2	
	13	200	80	4	
		Post-induction phase			
	22	—	—	12	
1	26-47	—	—	(7 x) 20	5 x 4
	52	100	40	—	
2	54-64	—	—	(3 x) 20	
	66	140	40	—	
	71-85	—	—	(5 x) 20	
3	87	120	40	—	
	93-107	—	—	(4 x) 20	
	109	160	40	—	
4	114-128	—	—	(5 x) 20	
	130	180	100	—	
	132-149	—	—	(6 x) 20	
5	151	180	100	—	
	153-170	—	—	(6 x) 20	
	172	200	100	—	Reducing
6	176-191	—	—	(5 x) 20	
	193	160	80	—	
7	195-219	—	—	(8 x) 20	
	221	160	80	—	0.5 x 0.5 x 0.3
	223-254	—	—	(10 x) 20	
8	256	160	20	—	Impalpable
	257	End of IT treatment; subsequent IV and SC treatment not shown.			CR
Total					
No. of applications		17 x	15 x	64 x	
ME dose		2 640	792	1 198.4	

Abbreviations: CR, complete response; IT, intratumoral; IV, intravenous; ME, mistletoe extract; PCMZL, primary cutaneous marginal zone lymphoma; SC, subcutaneous.

[a] Month and day (interval) of treatment; mode, dose, and number of ME applications.

[b] Infused in 250 mL sodium chloride 0.9% over 60-90 minutes.

apy felt gentler and simply like the right thing to do. The treatment itself, whilst challenging, confirmed my feeling that it was the bedrock, the main stay [sic] *of being healed.*

DISCUSSION

The primary cutaneous B-cell lymphoma of 2 patients regressed after administration of a combination of SC, IV, and IT applications of high-dose, fever-inducing ME treatment. The rationale for the combination was to optimize immune responses as currently understood to elicit fever and to apply the principle of "in situ" vaccination with IT application. In one patient, WBHT was added to draw on the benefits of improved immune competence that is associated with fever-range hyperthermia.[29] Three and a half years since commencement, the patients remain in clinical remission.

With high dosage, especially local ME applications, tumor remissions have been reported repeatedly in a number of tumor types, including breast cancer, Merkel cell cancer, primary liver cancer, pancreatic cancer, and cutaneous squamous cell cancer.[25-27] Still, high-dose and combined IT, IV, and SC administration that aims to elicit febrile induction is uncommon and underreported.

The literature on ME treatment of lymphoma is limited compared to that of other tumor types. One retrospective study describes favorable outcomes, including a few remissions in a group of 61 patients with follicular non-Hodgkin's lymphoma treated with a low-lectin ME (Iscador Pini) either alone or combined with or on completion of chemotherapy.[30] Another retrospective study primarily investigated safety aspects of ME treatment in Hodgkin's and non-Hodgkin's lymphoma and found no risks.[31] Some case reports describe remission of non-Hodgkin's lymphoma under ME monotherapy,[32-35] including 2 in cutaneous T-cell lymphoma in children.[36,37] In these cases, the dosage was lower than in the cases reported here and applied mainly subcutaneously and only partly intravenously and intratumorally. At least one fever reaction was reported.

Preclinical studies with lymphoma cells and murine lymphoma models treated with ME, isolated MLs, recombinant ML, and other ME peptides have consistently shown antitumoral effects with tumor inhibition, inhibition of metastases, and survival benefit.[19,38-42] ME contain several cytotoxic ingredients, among them lectins and viscotoxins, which are particularly abundant in *Abnobaviscum fraxini*. When lectins are applied systemically, their cytotoxicity is moderated by serum proteins[43] and later by the occurrence of anti-ML antibodies;[44] hence, their cytotoxicity is to be expected, primarily with IT administration. However, a disease response could also be effected by an immunological mechanism, as has been demonstrated for ME repeatedly.[19,20] Furthermore, fever seems to have a role in tumor defense.[45] The impact of ME treatment cannot be easily ascertained when used concurrently with mainstream cancer therapy. Occasionally, however, patients postpone or decline recommended conventional treatment in favor of ME, and such cases allow evaluation of ME treatment alone. Two of these patients are described above; these are the only two cutaneous lymphoma cases treated at PAC with ME alone and are therefore unselected. The cases of 2 other patients from PAC who had cancer at other sites and were treated with ME monotherapy have been published previously.[27]

In lymphoma, spontaneous remission is estimated to occur in 5% to 20% of cases. It is sometimes of long duration[16,17,46,47] and often is associated with reducing an immunosuppressive treatment or condition; following fever, viral or bacterial infections, or vaccination; or after biopsy and following eradication of helicobacter

For more information on fever in cancer treatment, see page 92.

in gastric lymphoma.[17] In a small follow-up study observing patients over many years, spontaneous remissions were reported in 4 of 16 patients with PCFCL (one of them complete) and in 4 of 8 patients with PCMZL (none of them complete), all of whom had a relapse.[48] Although spontaneous remission could have played a role in the cases presented here, in the first of the cases presented , the lesions had grown progressively until commencement of ME treatment and then steadily decreased, with fluctuating treatment-related inflammatory responses. In the second case, the lesion resolved after initial treatment-related increase and with some delay, which is a known response pattern in ME-associated tumor remissions.[26,30] Therefore, a mere coincidence is unlikely, especially as the 2 cases are unselected (meaning that they were not selected from a larger group of patients with cutaneous lymphomas treated with ME but were the only patients with cutaneous lymphonas treated in this way) and represent the only patients with PCBCL from PAC that had been treated with ME monotherapy. One also has to consider that the fever-induction ME treatment is likely to upregulate just those mechanisms implicated in the frequent spontaneous remission described for lymphoma.

Two further case publications on ME treatment of a related entity, CD30+ T-cell lympho-proliferation, reported complete regression of multiple and active cutaneous and nodal disease.[37,38] In one case, treatment consisted of low-dose IV (3 infusions of 0.02 mg, 0.2 mg, and 2 mg) and SC (up to 2 mg twice a week) without fever or site responses, with a noticeable disease response within 1 week and durable (30 months) complete response (CR) within 4 weeks. The second case was treated with primary fever intent (38°C), IT, and SC, and had a dose-dependent partial response and CR that relapsed with a lower-dose ME but regressed again with dose increase.

A differentiated appreciation of the singular components of the combined ME treatment—the specific role of fever and each of the specific contributions of SC, IT, and IV—and of the synergies is not possible given the current knowledge and require further research.

Although treatment was well tolerated and the safety observed is in accordance with other investigations on the safety of ME treatment in higher dosage,[28] this treatment should be reserved for use by physicians who have experience with ME application in higher dosages and IT/IV until further investigations have explored the role of high-dose, fever-inducing ME in cancer and its safety in more detail.

CONCLUSION

High-dose, fever-inducing mistletoe treatment seems to have beneficial effects in two cases of primary cutaneous B-cell lymphoma. Further research is needed to investigate antitumor effects, potential mechanisms of action, best mode of application, and the associated safety and efficacy.

Consent

Written informed consent was obtained from both patients for publication of the report and the accompanying Figures. They both read the final version of the paper and confirmed its contents.

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