CASE REPORT

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

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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 lymphomas. Case Report: Two patients with primary cutaneous B-cell lymphoma (pT2bcN,M, follicle center and pT2acN,M, 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.

Key Words
Mistletoe treatment, lymphoma, primary cutaneous B-cell lymphoma, fever, PCBC1, PCFCL, PCMZL, cancer, tumor

Conflict of Interest
The authors declare no competing interests.

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, 1:100,000); 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%; 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 prednisolone [CVP]), or

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 pT2bcNxM0 y zona marginal pT2acNxM0) 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.
immunotherapy with interferon-α.\textsuperscript{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 \textit{Borrelia burgdorferi} infection.\textsuperscript{8–12} They respond to immunological treatments like intrallesional injections of interferon-α\textsuperscript{13} or adenovirus-encoding interferon-γ, which can even lead to remission in non-injected distant lesions.\textsuperscript{14} Survival in systemic lymphoma correlates with tumor-infiltrating immune cells,\textsuperscript{15} and for the occasionally observed spontaneous regressions of non-Hodgkin's lymphoma, immunologic mechanisms have been proposed.\textsuperscript{16,17}

Mistletoe extract (ME) is a whole plant remedy derived from \textit{Viscum album} L, a hemi-parasitic shrub; it is widely used for complementary cancer treatment, especially in Europe, in conjunction with conventional therapy.\textsuperscript{18} A variety of biologically active compounds have been isolated from ME, including mistletoe lectins (MLs), viscotoxins, oligo- and polysaccharides, and others.\textsuperscript{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\textsuperscript{19,20}), and several compounds (ML in particular) are cytotoxic with established apoptosis-inducing effects.\textsuperscript{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.\textsuperscript{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.\textsuperscript{22–24} However, these observations have been reported only in case series and case reports.\textsuperscript{25–27} 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.\textsuperscript{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 pT1bN0M0. 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, 2 cycles of adriamycin and vincristine, 2 cycles of ifosfamide and etoposide, and 2 cycles of dexamethasone and vincristine, indicated to be necessary for her stage. She was also given a 9-month maintenance dose of ME 30 days after the end of chemotherapy.

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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](image-url) Primary cutaneous B-cell lymphoma in July 2008. Posterior lesion left lower leg.

![Figure 4](image-url) Primary cutaneous B-cell lymphoma in July 2008. Anterior lesion left lower leg; surrounding satellites not showing clearly.

| Month | Day or Interval | IV Treatmentb | IT (no. of sessions, if > 1) | SC Treatment | WBHT |
|-------|----------------|---------------|-----------------------------|--------------|------|
| 0     | 1              | 40            | —                          | —            | —    |
| 0     | 2              | 80            | —                          | —            | —    |
| 0     | 3              | 160           | 1                          | 10           | 1    |
| 0     | 4              | —             | 4                          | 20           | —    |
| 0     | 8              | 160           | 10                         | 30           | —    |
| 11    | 11             | 160           | 20                         | 20           | —    |
| 15    | 15             | 160           | —                          | 40           | —    |

| 16    | —              | 40            | —                          | 40           | —    |
| 18    | 16            | —              | (x 40)                      | —            | —    |
| 21-28c| —              | (x 40)        | —                          | —            | —    |
| 25    | 200            | —              | —                          | —            | —    |
| 1     | 29-35          | —              | (2 x 40)                    | —            | —    |
| 32    | 200            | —              | —                          | —            | —    |
| 36-42 | —              | —              | —                          | —            | —    |
| 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                         | —            | —    |

| 18    | —              | 240c          | —                          | —            | No. 3 |
| 58    | 200            | —              | —                          | —            | No. 4 |
| 61    | —              | —              | —                          | —            | —    |
| 64-70 | —              | (2 x 40)       | —                          | —            | —    |
| 67    | 200            | 320c          | (2 x 40)                    | —            | —    |
| 71-77 | —              | (2 x 40)       | —                          | —            | —    |
| 74    | 200            | —              | —                          | —            | —    |
| 78    | —              | 320c          | 40                         | —            | —    |
| 79    | 200            | —              | —                          | No. 5        | —    |

| 3     | 85-91          | —              | —                          | 40           | No. 6 |
| 88    | 200            | 320c          | (2 x 40)                    | —            | —    |
| 92-98 | —              | (2 x 40)       | —                          | —            | —    |
| 95    | 200            | —              | —                          | —            | —    |
| 99    | —              | 320c          | —                          | —            | —    |
| 100   | 200            | —              | —                          | —            | —    |
| 103-112| —            | (2 x 40)      | —                          | —            | —    |
| 109   | 200            | —              | —                          | —            | —    |
| 113-119| —            | (2 x 40)      | —                          | —            | —    |
| 116   | 200            | —              | —                          | —            | —    |
| 4     | 120            | —              | 20                         | —            | —    |
| 127-140| —            | (2 x 40)      | —                          | —            | —    |
| 135   | 200            | —              | —                          | —            | —    |
| 5     | 141-161        | —              | (5 x 40)                    | —            | —    |
| 162   | —              | 360c          | —                          | —            | —    |
| 163   | 200            | —              | —                          | —            | —    |
| 6     | 169-182        | —              | (3 x 40)                    | —            | —    |
| 178   | 200            | —              | (2 x 40)                    | —            | —    |
| 183-189| —            | (2 x 40)      | —                          | —            | —    |
| 190   | —              | 400c          | —                          | —            | —    |
| 191   | 200            | —              | —                          | —            | —    |
| 197-210| —            | (2 x 40)      | —                          | —            | —    |
| 204   | 200            | —              | —                          | —            | —    |
| 211-231| —            | (2 x 40)      | —                          | —            | —    |
| 233   | —              | 400c          | —                          | —            | —    |
| 234   | 200            | —              | —                          | —            | —    |
| 272   | —              | 400c          | —                          | —            | —    |
| 279-369| —            | (2 x 40)      | —                          | —            | —    |
| 338   | 200            | —              | —                          | —            | —    |
| 12    | 370            | —              | 240c                       | —            | No. 12|
| 371   | 200            | —              | —                          | —            | No. 12|
| 372   | End of IT treatment; subsequent IV and SC treatment | — | — | — | — | — |

| 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.

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

c Infused in 250 mL sodium chloride 0.9%, over 60-90 minutes.

d IT distributed over both lesions.

e Treatment period of 1 or more weeks during which SC injections were given.

f 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.
**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, pT1a, N1, M0, 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’ 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 scar formation. No hypersensitivity and no signs or symptoms of autoimmune reactivation were observed. After 6 months, the patient consistently reported improved vitality and well-being.

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-
Case Report

Table 2  Treatment Schedule (08/09-08/04/09) and Tumor Size of Patient With PCMZL.

| ME Dosage (mg) Per Application | Day or Interval | IV Treatment* | IT Treatment (no. of sessions, if > 1) | SC Treatment | Tumor Size (cm) | Palpation |
|-------------------------------|----------------|----------------|---------------------------------------|--------------|----------------|----------|
| Induction phase               |                |                |                                       |              |                |          |
| 0                             | 1              | 40             | —                                    | —            | 3 x 2          |          |
| 2                             | 2              | 80             | —                                    | 0.2          |                |          |
| 3                             | 4              | 160            | —                                    | —            |                |          |
| 4                             | 5              | 200            | 2                                    | 0.2          |                |          |
| 5                             | 7              | 200            | 20                                   | —            |                |          |
| 10                            | 10             | 200            | 40                                   | 2            |                |          |
| 13                            |                |                |                                       |              |                |          |
| Post-induction phase          |                |                |                                       |              |                |          |
| 22                            | 1              |                |                                       |              |                |          |
| 1                             | 26-47          | —              |                                       |              |                |          |
| 2                             | 54-64          | —              | (7 x 20)                             |              | 5 x 4          |          |
| 3                             | 66             | 140            | 40                                   |              |                |          |
| 3                             | 71-85          | —              | (5 x 20)                             |              |                |          |
| 4                             | 87             | 120            | 40                                   | —            |                |          |
| 3                             | 93-107         | —              | (4 x 20)                             |              |                |          |
| 4                             | 109            | 160            |                                       |              |                |          |
| 4                             | 114-128        | —              | (5 x 20)                             |              |                |          |
| 5                             | 130            | 180            | 100                                  |              |                |          |
| 6                             | 132-149        | —              | (6 x 20)                             |              |                |          |
| 5                             | 151            | 180            | 100                                  |              |                |          |
| 6                             | 153-170        | —              | (6 x 20)                             |              |                |          |
| 6                             | 172            | 200            | 100                                  |              |                |          |
| 6                             | 174-191        | —              | (5 x 20)                             |              |                |          |
| 7                             | 193            | 160            | 80                                   |              |                |          |
| 7                             | 195-219        | —              | (8 x 20)                             |              |                |          |
| 8                             | 221            | 160            | 80                                   | 0.5 x 0.5 x 0.3 x |              |          |
| 8                             | 223-254        | —              | (10 x 20)                            |              |                |          |
| 8                             | 256            | 160            | 20                                   |              | Impalpable     |          |
| 8                             | 257            |                |                                       |              |                |          |
| 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.

* Month and day interval of treatment; meds, dose, and number of ME applications.

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

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 intra-tumorally. 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 *Ammobaviscum fraxini*. When lectins are applied systemically, their cytotoxicity is moderated by serum proteins43 and later by the occurrence of anti-ML antibodies; 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.43 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.44

In lymphoma, spontaneous remission is estimated to occur in 5% to 20% of cases. It is sometimes of long duration16,17,46,47 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...
in gastric lymphoma.\textsuperscript{10} 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.\textsuperscript{45} 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.\textsuperscript{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 lymphomas 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.\textsuperscript{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 remission (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,\textsuperscript{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.

\textbf{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.

\textbf{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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