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Successful treatment of classic Kaposi sarcoma with low-dose intramuscular immunoglobulins

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MADAM, Kaposi sarcoma (KS), a malignant multilocular angioproliferative disease, is aetiologically linked to human herpes virus (HHV)-8 infection and immune dysfunction.[1] There is no standard therapy.[1,2] Various local treatments, including cryotherapy, radiotherapy, intralesional chemotherapy, laser therapy and topical alitretinoin may be effective but limited in patients with multiple lesions.[1,2] Systemic treatment options including interferon alfa, antiangiogenic strategies such as thalidomide or sirolimus, and cytotoxic therapies, such as vinca alkaloids, bleomycin, etoposide, taxanes and anthracyclines are used in palliative settings.[1–4] Especially, liposomal anthracyclines may be beneficial in widespread disease.[2,5] However, chemotherapy may aggravate pre-existing immunosuppression and may be limited by side-effects.

A 63-year-old Turkish woman presented with various manifestations of classic KS on the lower legs, ears, lower back and palms that had developed 6 months previously, the largest with a size of 8 × 4 cm on the right lower leg (Fig. 1a). Histology showed patch, plaque and nodular lesions of KS. The tumours were characterized by proliferation of atypical spindle cells lining vascular slits containing erythrocytes, and a sparse infiltrate of lymphocytes and plasma cells (Fig. 2a, b). As demonstrated by immunohistochemistry, the spindle cells expressed the lymphatic endothelium marker podoplanin (Fig. 2c). In addition, HHV-8 was detected in the tumour cells immunohistochemically (Fig. 2d) and by polymerase chain reaction (PCR). In the patient's serum, HHV-8 DNA was detectable by PCR analysis and highly positive anti-HHV-8 IgG levels by fluorescent antibody tests. Further laboratory and radiology diagnostics were within normal limits and excluded human immunodeficiency virus or extracutaneous involvement.

The patient refused radiation therapy of the lower leg or other suggested conventional therapy. We started a therapeutic attempt with intramuscularly administered Beriglobin® (BG; CSL Behring, Marburg, Germany), a preparation of globulins containing antibodies normally present in adult human blood. We injected 5 mL BG (800 mg immunoglobulin) according to the dose recommended for pre-exposure prophylaxis of hepatitis A infection. Four weeks after the first administration a marker lesion on the right lower leg had already lightened significantly (Fig. 1b). We continued the treatment with seven more injections every 4 weeks. After 6 months, complete remission was achieved (Fig. 1c) and confirmed histologically. As demonstrated by podoplanin stainings only a few residual lymphatic vessels without formation of spindle cells were present (Fig. 2e) and HHV-8 was no longer detectable immunohistochemically. Five months later, the disease recurred on the left lower arm and the right ear (Fig. 1d). Another course of intramuscular immunoglobulin injections was started, again resulting in complete remission within 6 months (Fig. 1e, f). Therapy was continued for another 3 months. The patient continued to have high anti-HHV-8 titres, but HHV-8 DNA became undetectable in the patient's serum.

The batch of BG that was used was analysed for HHV-8-specific IgG by indirect immunofluorescence applying fluorescein–isothiocyanate-conjugated antihuman IgG1–4 monoclonal mouse antibodies. Surprisingly, the immunoglobulin preparation contained a high concentration of anti-HHV-8 IgG1 (titre 1 : 600) and IgG3 (titre 1 : 600) antibodies. This was unexpected, as the donors originated from Germany, Austria and the U.S.A. For Germany and other Western European countries HHV-8-seroprevalences of only 2–3% have been reported.[6]

After a disease-free interval of 4 years without any treatment the patient relapsed with KS manifestations on the lower legs, the right ear and the tip of the nose (Fig. 1g). Remarkably, together with the clinical relapse HHV-8 DNA again became detectable in the patient's serum. Again, we administered intramuscular BG. The tumours responded considerably within 5 weeks after the first injection (Fig. 1h) and completely resolved after 3 months (Fig. 1i). As complete response was achieved again this batch of BG was not analysed for anti-HHV-8 antibodies. During the whole time of immunoglobulin treatment, no side-effects were observed.

As reported earlier, a patient with polymyositis and iatrogenic KS reached stable regression after shifting from immunosuppressive therapy to high-dose intravenous immunoglobulins.[7] However, it remained unclear whether this was due to discontinuation of the immunosuppression or a direct therapeutic effect of the immunoglobulins. In patients with iatrogenic KS, tumour regression has been observed after the withdrawal of immunosuppressive therapy.[8,9] In addition, the development of KS under combined therapy with immunosuppressive drugs and immunoglobulins has been reported.[10] To our knowledge, successful therapy of KS using low-dose intramuscular immunoglobulins, an immunological approach presumably targeting the HHV-8 infection as a major aetiopathological factor, has not yet been described. BG, which in contrast to many other potential treatments does not lead to

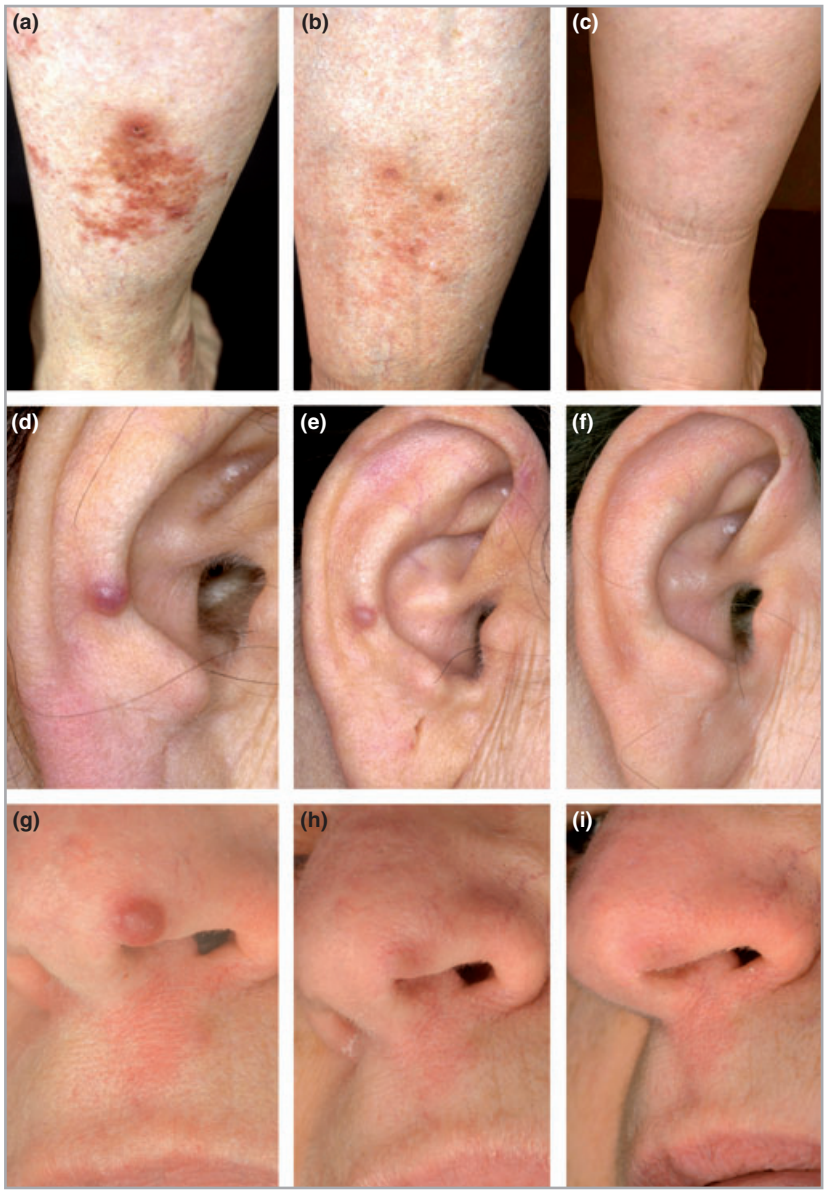

Fig 1. Classic Kaposi sarcoma with a marker lesion on the right lower leg (a), improvement within 4 weeks (b), and complete remission within 6 months (c), after initiation of a low-dose intramuscular immunoglobulin therapy with Beriglobin® (BG). Recurrence on the right ear 5 months later (d), response after 5 weeks (e), and complete remission after 4 months (f), of another course of BG treatment. Relapse after a 4-year disease-free interval without any treatment on the tip of the nose (g). Rapid improvement within 5 weeks (h), and complete remission within 3 months (i), after reintroduction of BG treatment.

further immunosuppression, might be a well-tolerated and relatively low-priced therapeutic option. At present in Germany, one dose (5 mL) of BG costs about €60. In our patient, HHV-8 DNA became undetectable in the blood during clinical remission, whereas recurrence was accompanied by viraemia. Because our patient had high titres of anti-HHV-8 antibodies, one might speculate that BG had substituted a lack of sufficiently working antibodies. In any case, the response of KS to low-dose immunoglobulin has to be confirmed by further investigations.

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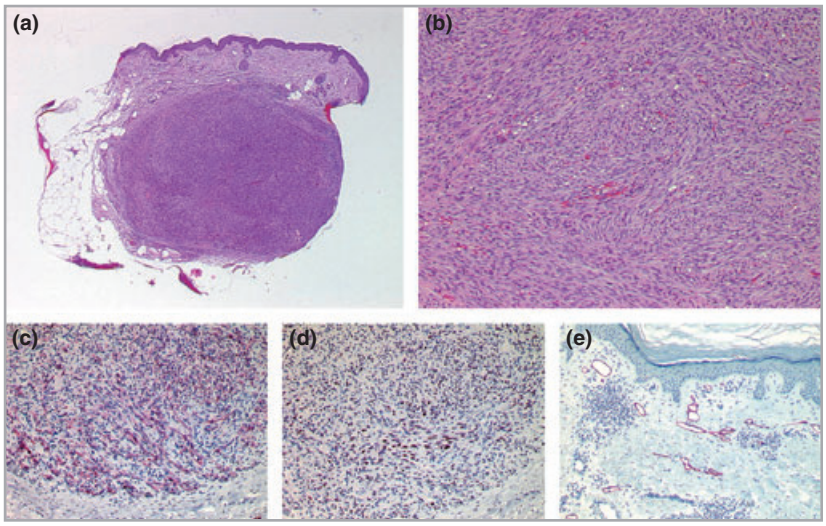

Fig 2. Haematoxylin and eosin staining of a nodular Kaposi sarcoma lesion with proliferation of miniature vessels in the dermis, formations of atypical spindle cells lining vascular slits with erythrocytes, and an infiltrate of lymphocytes and plasma cells (a, b). Immunohistochemically, the lymphatic marker podoplanin (c) and the human herpes virus (HHV)-8 latent nuclear antigen (d) were detectable in the spindle cells. After complete response of the tumour only a few residual lymphatic vessels without formation of spindle cells were present as demonstrated by podoplanin stainings (e) and HHV-8 was not detectable anymore.

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A dermal equivalent can be developed from fibroblast culture by means of a high concentration of serum

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MADAM, Previously, in order to approximate the human dermis *in vivo* several models of dermal equivalents have been developed *in vitro*. Various materials such as bovine collagen, glycosaminoglycan, human allogenic dead dermis and synthetic polymers have been used.[1–4] However, previous models have some drawbacks because they contain exogenous materials, which may be expensive, difficult to obtain, and a possible source of infection and rejection for clinical application. To solve the problems, we have developed a dermal equivalent by culturing post-confluent dermal fibroblasts alone in serum containing medium treated with several supplements.[5,6] Other groups have also reported *de novo* synthesis of human dermis *in vitro* in the absence of a three-dimensional scaffold.[7,8] In a preliminary study, we found that serum might be essential for the construction of dermal equivalents. Thus, in this study, we investigated the effects of serum on the construction of a dermal equivalent.

Dermal fibroblasts were isolated from human foreskins and were then cultured in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS). This study was performed according to the principles of the Declaration of Helsinki. The procedure used to obtain human foreskins received prior approval from the Samsung Medical Center Institutional Review Board. Dermal fibroblasts were seeded at a density of 10^5 cells per well in six-well dishes and cultured