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## Case report

# Anaphylaxis to viscotoxins of mistletoe (*Viscum album*) extracts

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**Background:** Extracts of mistletoe (*Viscum album*) are used in many countries for adjuvant cancer therapy. These extracts contain mistletoe lectins and viscotoxins that are supposed to have immunostimulating and cytotoxic effects, respectively. The treatment is usually well tolerated.

**Objective:** To report a case of severe anaphylaxis secondary to mistletoe extract administration with demonstrable anti-IgE antibodies to mistletoe.

**Methods:** Skin prick tests, basophil histamine release, basophil activation test, and immunoblotting were performed to characterize the pathophysiology of this reaction.

**Results:** The patient had immediate-type skin prick test reactions to the whole commercial preparation and to its mistletoe extract component. A histamine release test and a flow cytometric basophil activation test performed with the patient's peripheral blood leukocytes by incubation with the mistletoe extract yielded a concentration-dependent histamine release and expression of the activation marker gp53 in up to 98% of anti-IgE-positive cells. Immunoblotting revealed IgE binding to 5-kDa proteins of mistletoe in the patient's serum, which corresponds to the molecular weight of viscotoxins. The results of all these tests were negative in controls.

**Conclusions:** Until now, anaphylaxis to mistletoe extracts has been only rarely reported. In our patient, viscotoxin specific IgE evidently had induced an anaphylactic reaction.

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## INTRODUCTION

Mistletoe (*Viscum album*) is a semiparasitic plant that grows primarily on hardwood trees (eg, oak and apple).<sup>1</sup> Its use as an herbal remedy dates as far back as Hippocrates. At the beginning of the 19th century, Rudolf Steiner<sup>2</sup> proposed that mistletoe be used in the treatment of malignancies. Currently, extracts of mistletoe are produced industrially and are used in anthroposophically oriented complementary medicine as adjunctive measures against malignancies.<sup>3</sup>

Mistletoe preparations contain various ingredients; the main antineoplastic effects are attributed to mistletoe lectins and viscotoxins. The viscotoxins (A1, A2, A3, B, 1 PS, and UPS) represent a group of basic low-molecular-weight proteins (5 kDa), which are thought to have cytotoxic effects.<sup>4</sup> Mistletoe lectins (ML-I, ML-II, and ML-III) are glycoproteins with a molecular weight between 50 and 115 kDa.<sup>5</sup> In addition to their cytotoxic effects, they might also be immunostimulants.

There is no strong scientific evidence that mistletoe might be effective against cancer. A systematic review of randomized clinical trials that used mistletoe to treat malignancies concluded that most of the studies were flawed by weak-

nesses and that efficacy of this treatment is not yet definitely established.<sup>6</sup>

Administration of mistletoe is generally well tolerated, with only mild adverse effects (eg, local reactions at injection site).<sup>7</sup> Severe adverse effects, including anaphylaxis, are rare, and to our knowledge, only 2 reports on a total of 4 patients with probable IgE-mediated anaphylaxis have been described in the literature.<sup>8,9</sup> We report a case of severe anaphylaxis secondary to mistletoe extract administration with demonstrable IgE antibodies to mistletoe.

## CASE REPORT

A 59-year-old woman with no medical history of atopy received injections of a mistletoe preparation (Iscador M c. Hg 1 mg; Weleda, Schwaebisch-Gmünd, Germany) and cyanocobalamin (vitamin B<sub>12</sub>-Depot-Injektapas, Pascoe, Giessen, Germany) biweekly for more than 2 years as an adjunctive antineoplastic therapy after colon cancer had been treated by hemicolectomy and chemotherapy. Otherwise, she took a hormone substitution because of menopause and thyroid hormones due to a cold node in the thyroid.

The injections of cyanocobalamin and mistletoe were tolerated for 2 years without any adverse effects. However, 2 months before her presentation in our clinic, she had developed generalized urticaria, swelling of the lips and tongue, nausea, vomiting, and shortness of breath within 10 minutes after administration of the mistletoe and the cyanocobalamin

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preparations. Emergency treatment was performed by an emergency physician. Vital signs were measured immediately (blood pressure, 110/80 mm Hg; pulse, 70/min; respiratory rate, 12/min; oxygen saturation as measured by pulse oximetry, 96%), and the patient was treated with intravenous dimethindene maleate, prednisolone, and metoclopramide. Subsequently, she was admitted to a hospital for further monitoring, and after 1 day she had completely recovered without any sequelae.

Skin prick tests with 1% and 10% undiluted Iscador M c. Hg 1 mg (which contains mercury D10) and the undiluted cyanocobalamin preparation were performed. There were no immediate- or delayed-type skin reactions to the cyanocobalamin preparation. To Iscador M c. Hg 1 mg, there was a concentration-dependent immediate-type test reaction (wheal diameter was 3 mm with the 1% preparation, 4 mm with the 10% preparation, and 6 mm with the undiluted preparation). Additional skin prick tests with a mistletoe extract without additives and a solution that contained mercury D10 (both supplied by the manufacturer) yielded a strongly positive (wheal diameter, 6 mm) immediate-type test reaction only to the mistletoe extract. In every examination, saline and histamine served as negative and positive controls, respectively. Skin prick tests with common allergens (grass pollen, house dust mites, birch pollen, cat and dog dander, latex) showed no immediate- or delayed-type test reactions in the patient.

Subsequently, we performed basophil histamine release and basophil activation tests by exposing the patient's peripheral blood leukocytes to different concentrations (0.002, 0.02, 0.2, 2.0, 20.0, and 200.0  $\mu\text{g/mL}$  and 2.0 mg/mL) of the mistletoe extract. Mistletoe-induced histamine release was concentration dependent and reached up to 100% of the total histamine content (Fig 1). A similar result was found in the flow cytometric basophil activation test, because expression

of gp53 (CD63) was found on up to 98% of anti-IgE-positive cells (Fig 2). Gel electrophoretic separation of the constituents of the mistletoe preparation and subsequent immunoblotting using the patient's serum revealed IgE binding at a molecular weight of approximately 5 kDa, corresponding to the molecular weight of viscotoxins (Fig 3).

The results of skin prick tests with Iscador M c. Hg 1 mg and Iscador M were negative in 10 controls. Histamine release tests, basophil activation tests, and immunoblotting were performed additionally in 2 atopic controls; all the results were negative. When the formerly used cyanocobalamin preparation was administered intravenously in fractionated doses, it was tolerated without any adverse effects. Based on the patient history and the test results, we finally diagnosed an IgE-mediated anaphylaxis to viscotoxins of mistletoe.

## DISCUSSION

Severe adverse effects to mistletoe preparations have been only rarely reported. The Drug Commission of the German Medical Profession reported in 1997 several spontaneous communications concerning adverse effects of mistletoe treatment, ranging from headaches, elevated body temperature, and local reactions at the injection site to full anaphylactic shock.<sup>7</sup> Only a few case reports that address the pathophysiology of anaphylactic reactions to mistletoe have been described in the literature. Hutt et al<sup>8</sup> reported 3 cases of anaphylaxis to mistletoe injections. In 2 of the 3 patients, the results of skin testing with *V. album* were positive by either prick or intradermal testing. Intradermal testing provoked systemic symptoms in 1 of the 2 patients. Pichler and Angeli<sup>9</sup> described a patient who also had an anaphylactic reaction after mistletoe injections but no immediate or delayed skin reactions to mistletoe. However, the results of a lymphocyte

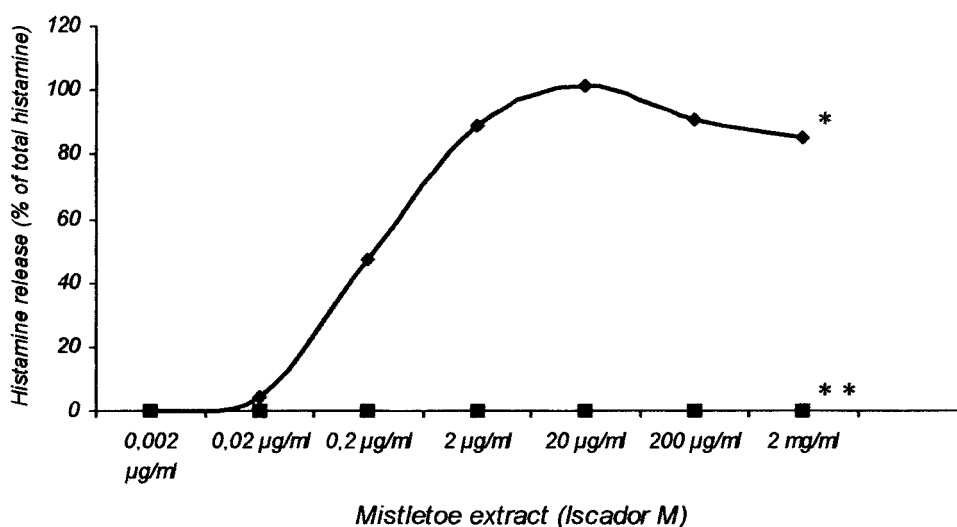


Figure 1. Histamine release from the peripheral blood leukocytes of the patient (asterisk) and 2 negative controls (double asterisks) on exposure to Iscador M (*Viscum album*).

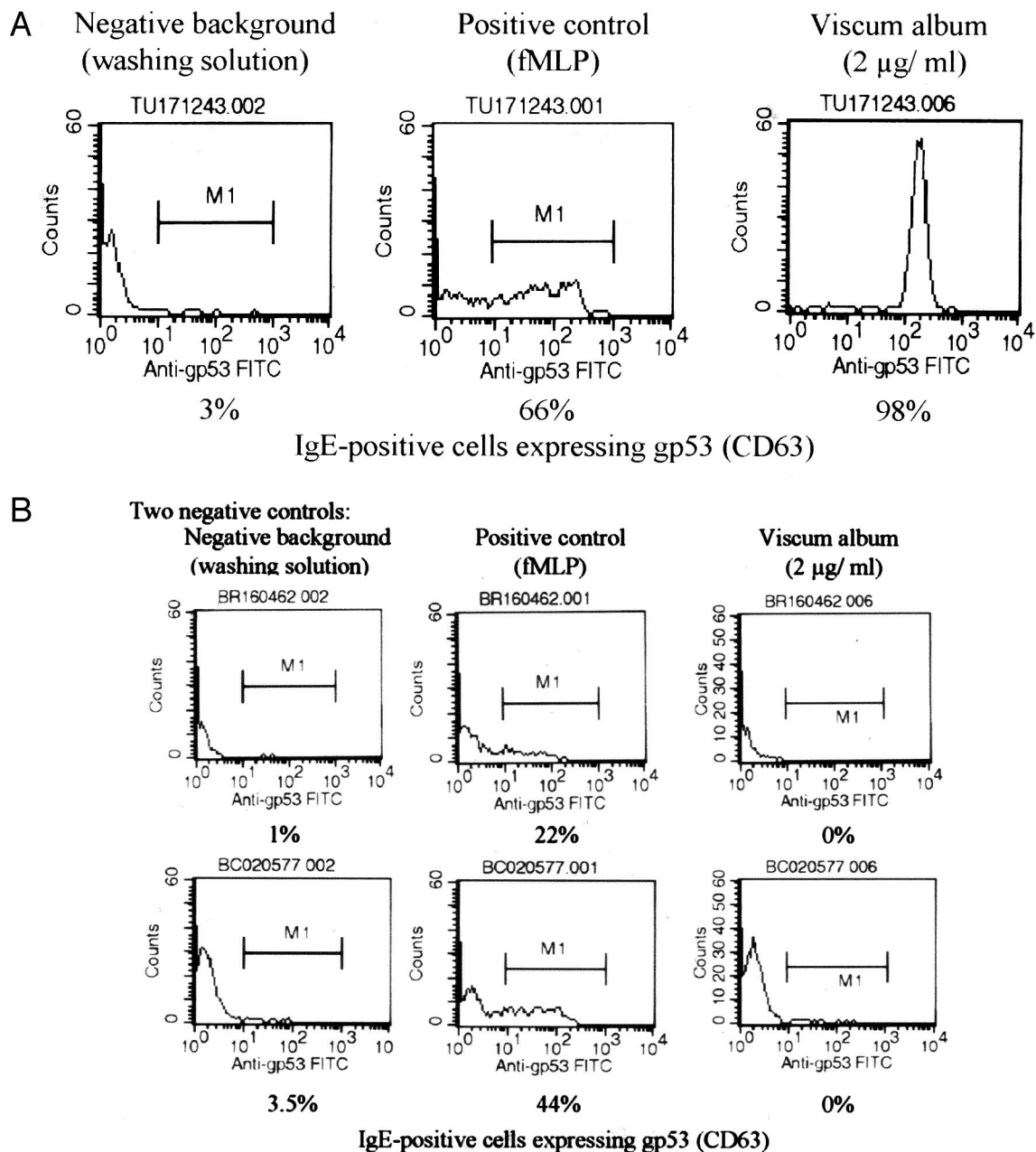


Figure 2. Basophil activation test with 2  $\mu$ g/mL of mistletoe extract (Iscador M). Expression of gp53 on 96% of anti-IgE-positive cells in the patient (A) compared with the results of 2 negative controls (B). FITC indicates fluorescein isothiocyanate; fMLP, *N*-formyl-methionyl-leucyl-phenylalanine.

proliferation test with cells for this patient were positive to mistletoe. In both reports, an allergic mechanism of the reactions was presumed. Klein et al<sup>10</sup> investigated 26 patients treated with a mistletoe extract for at least 18 weeks and found that ML-I and the viscotoxins A1, A2, A3, B, 1 PS, and UPS can induce the production of specific IgG, IgA, and IgE antibodies. The IgE antibodies against viscotoxins were directed only against viscotoxin B and occurred mainly be-

tween weeks 12 and 24. No anaphylactic reactions in these patients occurred.

In our patient, skin prick tests and in vitro tests with basophils (histamine release tests, basophil activation tests) yielded concentration-dependent reactions to *V. album*, suggesting an IgE-mediated mechanism. Among the many components of the mistletoe preparation, immunoblotting revealed proteins of approximately 5 kDa, which were

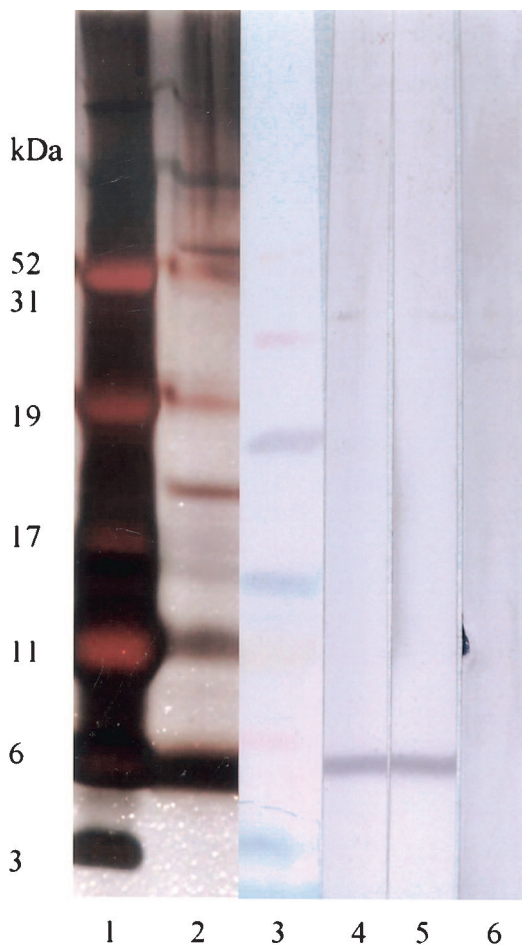


Figure 3. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis analysis for mistletoe proteins. Silver stain for total protein analysis and immunoblotting with the patient's serum show IgE binding to a 5-kDa protein. Electrophoresis: 1, standard marker; 2, mistletoe extract (Iscador M) undiluted; immunoblot: 3, standard marker; 4, Iscador M undiluted plus patient's serum undiluted; 5, Iscador M undiluted plus patient's serum diluted 1:2; and 6, Iscador M undiluted plus healthy control's serum undiluted.

recognized by IgE from the patient's serum. This 5-kDa band probably corresponds to viscotoxins. Rechallenge with mis-

tletoe extract was not performed in our patient based on the clear history of systemic reaction after the last exposure in conjunction with positive in vivo and in vitro diagnostic testing. Further support was gained with the negative test results and rechallenge with cyanocobalamin.

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