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Article *in* The Journal of Laryngology & Otology · February 2014

DOI: 10.1017/S0022215114000103 · Source: PubMed

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The Journal of Laryngology & Otology (2014), ***128***, *302–306*.

doi:10.1017/S0022215114000103

CLINICAL RECORD

The case for mistletoe in the treatment of laryngeal cancer

M SHAKEEL[1], A TRINIDADE[2], S GEIDER[3], K W AH-SEE[1]

[1]*Department of Otolaryngology, Aberdeen Royal Infirmary, Scotland,* [2]*ENT Department, James Paget Hospital, Great Yarmouth, England, and* [3]*Camphill Wellbeing Trust, Aberdeen, Scotland, UK*

Abstract

Introduction: Complementary and alternative medicine usage, though rising, remains largely devoid of a sound scientific basis; however, there is increasing evidence to support its use in cancer therapy.

Aim: To present the case of a patient with laryngeal carcinoma who made a full recovery following mistletoe therapy, despite failing to respond to chemoradiotherapy and salvage laryngectomy.

Design: Case report with relevant literature review.

Results: The patient developed extensive, unresectable stomal recurrence, and it was deemed appropriate to supply palliative care only. Following treatment with mistletoe extract injections after palliative radiotherapy, he recovered fully and was eventually discharged from care.

Conclusion: The benefit of mistletoe in laryngeal cancer treatment requires further investigation, and might be considered in selected patients, as an adjunct or when other conventional therapies have failed.

Key words: Mistletoe; Laryngeal Neoplasms; Carcinoma; Complementary Medicine

Introduction

Mistletoe extracts are commonly used for cancer patients, in whom they are claimed to improve survival and quality of life.[1] In Europe, extracts from *Viscum album*, the European white-berry mistletoe, are widely used to treat patients with cancer. The evidence that supports its use, however, is conflicting. Whilst mistletoe has a convincing role in improving cancer patients' quality of life and ability to cope autonomously with disease (via psychosomatic self-regulation),[2] and in combating the side-effects of cancer therapy,[3] the evidence regarding its role as an actual cure remains, to many authors, inconclusive.[1]

We present the case of a patient who, despite being deemed terminally ill from aggressive stomal recurrence of his laryngeal cancer, made a full recovery once conventional curative treatment was withdrawn and mistletoe treatment initiated.

Case report

A 68-year old, Caucasian, male smoker with a history of moderate wine intake was diagnosed with left, tumour stage 3, node stage 0, metastasis stage 0, transglottic, laryngeal squamous cell carcinoma (Figure 1). He received radical radiotherapy (55 Gy in 20 fractions) with concurrent single agent chemotherapy (cisplatin 100 mg/m^2).

One year later, and six months after the completion of chemoradiotherapy, multiple biopsies were taken at laryngoscopy due to persistent laryngeal oedema and hoarseness, though no obvious evidence of recurrence was seen. These biopsies confirmed carcinoma in situ; however, because of the patient's symptoms and the superficial nature of the biopsies, the multidisciplinary team concluded that chemoradiotherapy had failed. The decision was made to undertake surgery, and, after discussion with the patient, total laryngectomy was decided upon.

At nine months post-laryngectomy, the patient complained of pain on the left side of his stoma. Fullness was noted at the left side of the proximal trachea, but with no mucosal lesions in the stoma or in the pharynx. A magnetic resonance imaging (MRI) scan revealed left parastomal recurrence (3×3 cm) (Figure 2), and incisional biopsy of the mass confirmed squamous cell carcinoma recurrence.

The patient was offered further surgery to excise the recurrence. The procedure was carried out by a team of otolaryngology and cardiothoracic surgeons. Intra-operatively, the tumour was found to be much more advanced than the MRI scan had suggested. The tumour was encircling 75 per cent of the trachea and pharynx. There was significant retrosternal extension, with no plane of dissection behind the manubrium, and the necrotic tumour was extending across the midline to reach the right retroclavicular region. Despite extensive dissection, the tumour was deemed inoperable, and was therefore debulked with refashioning of the stoma.

Post-operatively, the patient was given palliative radiotherapy to the retrosternal region; this was well tolerated but stomal healing was slow.

At this stage, while the stomal wound was slowly healing, the patient consulted his local general practitioner, requesting to receive mistletoe treatment.

Three months post-radiotherapy, the patient received mistletoe therapy for his inoperable cancer. This was

Accepted for publication 2 October 2013 First published online 19 February 2014

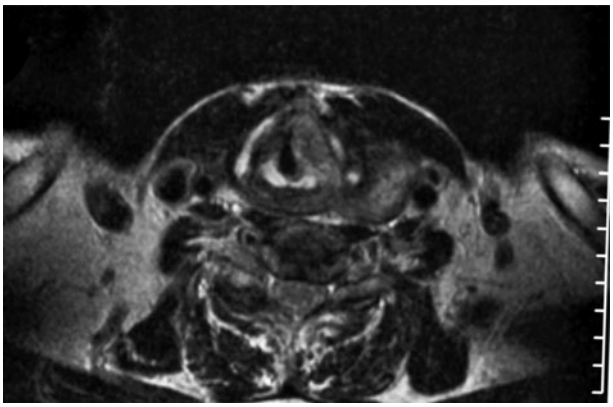

FIG. 1

Axial magnetic resonance imaging scan showing left transglottic laryngeal squamous cell carcinoma, staged as tumour three, node zero, metastasis zero.

administered as subcutaneous abdominal injections of Abnobaviscum Fraxini (Abnoba Heilmittel, Pforzheim, Germany) over the course of 72 months, between November 2006 and December 2012, by one of the authors (SG), a general practitioner and practitioner of anthroposophic medicine. (This branch of medicine is viewed by its practitioners as an integrative approach to disease which is an extension of the conventional medical model.) The patient's treatment regime is outlined in Table I. His general well-being during treatment was monitored and recorded at follow-up appointments using the Karnofsky performance scale, outlined in Table II. The patient was also followed up in the head and neck clinic; complete stomal wound healing was noted, together with continued general improvement.

Subsequently, the patient underwent secondary tracheoesophageal puncture and speaking valve insertion.

Thereafter, the patient was followed up every four months. His parastomal and mediastinal recurrences were seen to disappear completely. Over the seven years following initiation of mistletoe extract therapy, i.e. up to the time of writing, the patient continued to show no evidence of locoregional recurrence. At his last visit, in February 2013, the mistletoe injections were reduced to a short course twice yearly as he was deemed cancer-free both clinically and radiologically. In April 2013, follow-up MRI scans showed no residual parastomal or mediastinal disease (Figures 3 and 4), and the patient was discharged from our care.

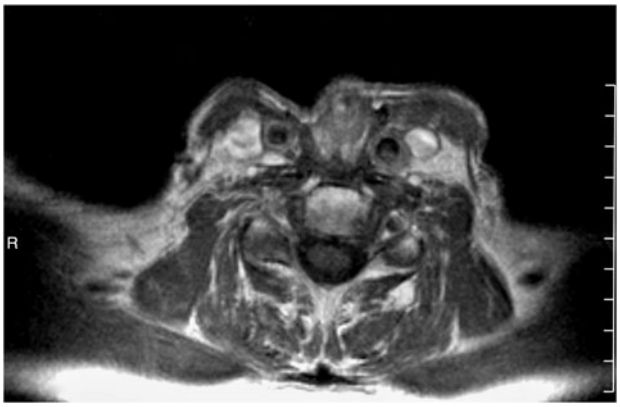

FIG. 2

Axial magnetic resonance imaging scan showing left parastomal recurrence of squamous cell carcinoma post-treatment. R = right.

Discussion

'Mistletoe' is the common name used for obligate hemi-parasitic plants in several families within the Santalales order. The name was originally used solely for the species *Viscum album*, or European mistletoe, the only species native to the UK and much of Europe. This plant may cause acute gastrointestinal problems if ingested, including stomach pain and diarrhoea, along with bradycardia. However, it is this species that is the centre of much research with respect to its extracts and their purported uses in the treatment of cancer.

Use of mistletoe as an anti-cancer agent was first popularised by the German Rudolf Steiner, who referred to mistletoe as a remedy for cancer. Steiner (the founder of anthroposophy) proposed that its physical and spiritual qualities supported re-establishment of the harmonious integration of the alleged four different entities of human existence in a patient. Whilst there was no scientific basis for his claims, much of the research into mistletoe's benefits has been conducted in Germany, where its use remains frequent.[1]

Mistletoe extracts are mainly prepared as aqueous solutions and are usually administered subcutaneously. The most commonly used commercial formulation is Iscador (Weleda, Ilkeston, UK), but other forms are available, including Abnobaviscum Fraxini (Abnoba Heilmittel), which has been used mainly in cancer therapy, as in our patient. The use of mistletoe extracts has been deemed safe,[4] although subcutaneous administration is known to carry a risk of inflammation at the injection site.[5]

The pharmacological properties of mistletoe have been studied at the cellular level. The active compounds in mistletoe are lectins and viscotoxins.[6] Phase one clinical trials have shown that recombinant mistletoe lectin (aviscumine), produced in *Escherichia coli,* has immunomodulatory and cytotoxic activity *in vitro* and in animal models, and can target tumour cells.[7] One suggested mechanism for these actions is induction of the production of potentially tumour-promoting cytokines such as interleukin-6.[4] In view of its abilities, mistletoe has been classified as a biological response modifier. Its antiproliferative, cytotoxic and immunomodulatory properties are dose-dependent; reported tumour remissions are associated with doses higher than the commonly recommended dosage, with intratumoural application and with accompanying fever, as in our patient. The latter is likely to be important in determining the dosage required to affect the clinical outcome. Orange *et al.*[8] have postulated that high-dose febrile induction therapy, in various combinations of intratumoural, subcutaneous and intravenous application, can affect disease response. In addition to immunomodulatory effects, high doses of mistletoe extract have cytotoxic properties and elicit immunogenic apoptotic and necrotic tumour cell death in a dose-dependent manner.

Whilst much of the anti-cancer effects of mistletoe has been described in breast, uterine and ovarian cancer, mistletoe extracts have been shown in some studies to target laryngeal cancer cells.[9]

The characteristics of the immune responses to these types of mistletoe extract applications require further research.

One of the main benefits of mistletoe seems to be psychosomatic,[2] and it may have more of a role in the holistic care of the cancer patient, at least in the short term.

TABLE I
LARYNGEAL STOMAL CANCER RECURRENCE TREATMENT REGIME WITH SUBCUTANEOUS ABNOBAVISCUM FRAXINI: SUMMARY

Day	Abnobaviscum Fraxini dose	Clinical effect	Concurrent analgesia	Patient experience
1*	2 mg	No local skin reaction at injection site, or systemic reaction; slight pyrexia only	Fentanyl patch 50 μg every 72 hr Diclofenac 50 mg po tds Paracetamol 1 g po qds Oral morphine 10 mg po prn	Anorexia (eating mainly soup); substantial weight loss; lethargy (walking only a few metres); fatigue; insomnia Karnofsky status = 50%
3	4 mg	No local or systemic reaction		
5	20 mg (deemed therapeutic dose)	Large local response: swelling to 15 × 15 cm, gradually reducing in size; pyrexia to 38.5°C		
7	2 mg 3-weekly, gradually ↑ over 2 mth to max of 20 mg 3-weekly	Slight local response over weeks: swelling to max 3 × 3 cm for up to 2 days	Days 39–69: paracetamol & oral morphine discontinued	Days 39–60: patient resumes playing golf (9 holes every 10 days) Karnofsky status = 70%
70	20 mg 3-weekly for 2 mth		Days 100–130: diclofenac discontinued	Day 71: patient plays 18 holes of golf Karnofsky status = 90%
130	3-weekly regime ↑ to 20-20-40 mg for 18 mth	Ongoing slight local response	Days 250–320: gradual reduction in fentanyl patch use	Days 330–480: return of appetite with gradual increase to normal weight Karnofsky status = 100%
670	3-weekly regime ↑ to 40-20-40 mg for 2 mth	Fading local response	Day 330: fentanyl discontinued	
730	3-weekly regime ↑ to 40-40-40 mg for 3 mth			
820	Regime ↓ to 40 mg 2-weekly for 15 mth			
1270	Break for 2 mth			
1330	40 mg weekly for 1 mth	Patient deemed tumour-free		

*Induction. Hr = hours; po = per orally; tds = thrice daily; qds = four times daily; prn = as required; ↑ = increased; mth = months; max = maximum; ↓ = decreased

TABLE II
KARNOFSKY PERFORMANCE SCALE

Status	Definition
100%	No symptoms
90%	Able to carry on normal activity; minor signs or symptoms of disease
80%	Able to carry on normal activity with effort; some signs or symptoms of disease
70%	Cares for self, unable to carry on normal activity or do active work
60%	Requires occasional assistance but is able to care for most of own needs
50%	Requires considerable assistance & frequent medical care
40%	Disabled; requires special care & assistance
30%	Severely disabled; hospitalisation indicated, although death not imminent
20%	Very ill; hospitalisation necessary; active supportive treatment required
10%	Moribund, fatal processes progressing rapidly
0%	Patient expired

Yet, mistletoe extract appeared to have benefited our patient, who had a stomal recurrence of laryngeal squamous cell carcinoma following chemoradiation and laryngectomy, a diagnosis with a poor prognosis. Whilst there is no conclusive evidence that mistletoe therapy cured his recurrence, clinical monitoring and recent MRI scanning confirmed complete resolution of recurrent cancer during this treatment. When taken in the context of his treatment time-line and declining prognosis, and against a background of increasingly robust research, our patient's response makes for a compelling case. While the contribution of his palliative radiation cannot be ascertained, alone it is unlikely to have been curative for an extensive local recurrence which had previously failed to respond to chemoradiation and surgery. It may be assumed that the mistletoe was the primary agent responsible for the reduction of mediastinal lymphadenopathy.

- **Mistletoe extract is a form of complementary and alternative medicine**
- **It may have a role in cancer management, acting via biological response modification**
- **It improves cancer patients' ability to autonomously cope with disease, via psychosomatic self-regulation**

Finally, our patient is one of an increasing number of patients in the UK who turn to complementary and alternative medicine, often as a first line of treatment for their ailments. The reasons for this choice are varied and include cost, the nature of the illness (acute versus chronic), gender, age, accessibility of complementary and alternative medicine, the publicly perceived safety and efficacy of therapies, failure of conventional medical interventions, dissatisfaction with modern health care, and cultural background. In the UK, there are currently an estimated 50 000 complementary and alternative medicine practitioners, 10 000 of whom are registered health care professionals. Featherstone *et al.*[10] surveyed the prescribing practice of 323 Scottish general practitioners and found that 60 per cent prescribed herbal medicines.[10] Clinicians must not only have an understanding of the various forms of complementary and alternative medicine currently available, their potential side effects, and their possible interactions with conventional medications, but must also be willing to accommodate patients' wishes and make allowances for complementary and alternative medicine use when recommending conventional therapies, or, as in our patient, when conventional therapies fail.

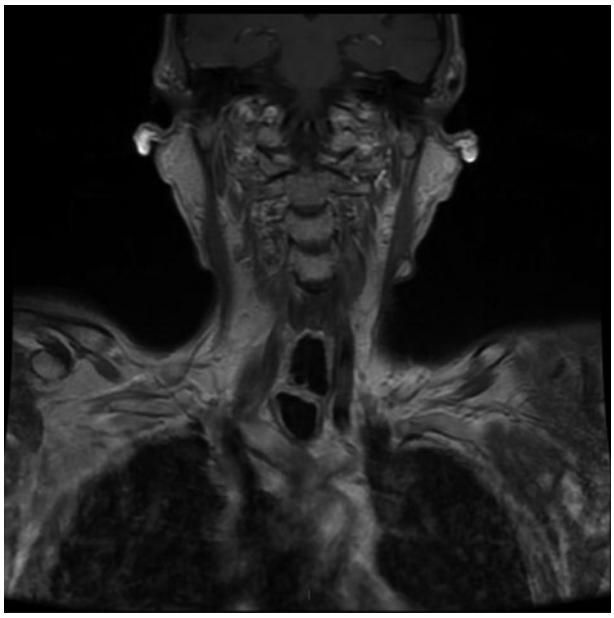

FIG. 3
Coronal magnetic resonance imaging scan showing resolution of stomal recurrence following mistletoe therapy.

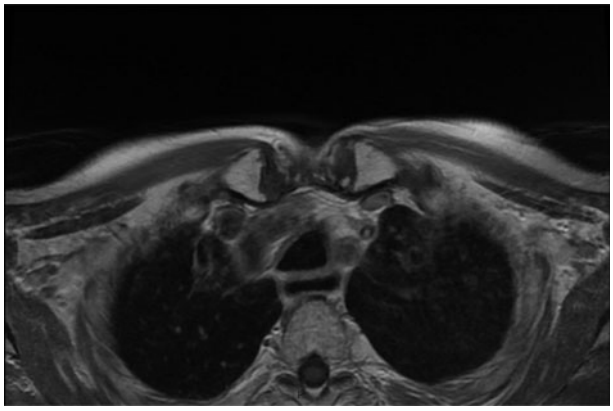

FIG. 4
Axial magnetic resonance imaging scan showing resolution of stomal recurrence following mistletoe therapy.

Conclusion

Mistletoe is a form of complementary and alternative medicine that is increasingly being considered in the management of cancer patients in many parts of Europe. Whilst its anticancer effect is still under scrutiny, it seems to be of benefit in the holistic management of cancer patients. In this setting, it has been shown to improve quality of life via a psychosomatic effect, but it may also have dose-dependent antiproliferative, cytotoxic and immunomodulatory properties that could cause tumour regression. It should be considered in the management of selected patients, including cases in which

conventional therapies are unlikely to provide a cure, especially as it has been shown to have a good safety profile regardless of the outcome.

Acknowledgements

The patient outlined in this case report has read the manuscript and agreed to its publication. He is quoted as saying,

> Nearly six years have passed since I was told I only had weeks to live. I hope my story will give cancer sufferers hope and the will to fight. I also wish for mistletoe's role in cancer therapy to be further investigated and more often recommended by cancer specialists.

We are grateful to the consultant oncologist Dr D Hurman for his help and advice in the preparation of this manuscript.

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Address for correspondence:
Mr Aaron Trinidade,
ENT Department,
James Paget Hospital,
Gorleston,
Great Yarmouth NR31 6LA, UK

E-mail: aarontrinidade@gmail.com

Mr A Trinidade takes responsibility for the integrity of the content of the paper
Competing interests: Dr S Geider prescribed and managed the mistletoe therapy