CASE REPORT

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Disappearance of an Advanced Adenomatous Colon Polyp after Intratumoural Injection with *Viscum album* (European mistletoe) Extract: a Case Report

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ABSTRACT

Background & Aim: Extracts of *Viscum album* (European mistletoe) have immune-stimulatory and cytotoxic effects, with trials showing a well-established effect on the quality of life and prolonged survival in patients with advanced pancreatic cancer. Regression of tumours following intratumoural injection with *Viscum album* extract has been documented in individual cases. However, its influence on colon polyps has not been investigated.

Case presentation: We present the case of a 78-year-old Caucasian male who had undergone hemi-colectomy for a stage IIIC colon cancer but who refused adjuvant chemotherapy. Five years later a newly detected high-grade dysplasia colon adenoma was discovered; however, the adenoma could not be resected endoscopically and the patient did not consent to surgery. Intratumoural injections with *Viscum album* L extract (*Quercus*; Iscador®Qu) were administered twice in an attempt to limit tumour growth. Eight months after the second intratumoural injection the adenoma had disappeared and biopsy revealed no intraepithelial dysplasia or adenoma.

Conclusions: This is the first report showing complete regression of a colon adenoma after intratumoural injection with *Viscum album* extract. Prospective studies should evaluate if the treatment effect is reproducible and if this approach could be a useful pre-operative measure for colon adenomas too large for endoscopic resection.

Key words: colon polyp – colorectal adenoma – *Viscum album* – European mistletoe – tumour regression.

INTRODUCTION

Adenomatous colon polyps are the cause of most colorectal cancers. At highest risk are adenomatous polyps (adenomas) with high-grade dysplasia [1]. A variety of techniques are used for colonoscopic polyp removal depending on polyp size and form, including mucosal or submucosal resection for larger sessile polyps [2]. Segmental resection may be required in more difficult cases.

Whole plant extract of *Viscum album* L. (Santalaceae; European mistletoe) is widely used as a complementary cancer treatment in Europe. Improvement of quality of life has been documented through many studies [3, 4]. A recent randomized controlled tiral (RCT) showed survival benefit in advanced pancreatic cancer [5]. Case reports have documented durable tumour regression [6-8]. In colorectal cancer, studies have shown benefits in terms of reduced cancer recurrence, survival in advanced cancer, and perioperative suppression of natural killer cells [9-11], but the specific effect of *Viscum album* extract on colon polyps has not been investigated. *Viscum album* extracts and several of its compounds are cytotoxic. Lectins from the extract, in particular, have strong apoptosis-inducing and immune stimulatory effects. These include *in vivo* and *in vitro* activation of monocytes/macrophages, granulocytes, natural killer cells, T-cells and dendritic cells, the induction of a variety of cytokines, and effects on tumoural angiogenesis [12-14].

Iscador®Qu (Weleda AG, Schwäbisch Gmünd, Germany) is an aqueous, lectin-rich extract of *Viscum album* L. grown on oak trees (*Quercus*) and is often used in the treatment of

colon cancer. Production involves fermenting the fresh plant with *Lactobacilli spp* and sterile filtration. Series 0 and 1 are packs of 7 1mL ampoules, typically given as subcutaneous injections 2 or 3 times weekly with ascending strength. Series 0 includes strengths 0.01mg/mL, 0.1mg/mL, and 1mg/mL. Series 1 includes strengths 0.1mg/mL, 1mg/mL, and 10mg/mL ampoules. "Iscador®Qu 5mg spezial" is a 5mg presentation with a lectin content of 391± 18.3 ng/mL [15]. Iscador®Qu is licensed for the German market by the German Federal Institute for Drugs and Medical Devices.We report the case of a male patient who refused resection of a colon adenoma and received intratumoural injections with *Viscum album* extract.

CASE REPORT

A Caucasian man had undergone hemi-colectomy at age of 78 years for an adenocarcinoma of the left colon. He had been otherwise healthy with normal weight, and had never smoked. He drank 1-2 glasses of wine a few evenings a week and ate a balanced diet with meat no more than twice per week. His father had died of colon cancer at age 86.

The carcinoma had infiltrated the surrounding fat tissue, had caused carcinomatous lymphangitis, and had metastasized to 21 regional lymph nodes (17 adjacent to the colon, 4 along blood vessels). It was classified as adenocarcinoma pT3 pN2 cM0 pL1 V0 R0 G3, stage IIIC. The patient's carcinoembryonic antigen (CEA) level was within normal limits (< 3 ng/mL). The patient refused adjuvant chemotherapy but accepted complementary treatment with *Viscum album* extract (Iscador®Qu). He injected Iscador®Qu subcutaneously every two days at home, beginning with one pack of Series 0, then with Series 1 in treatment cycles of 4 weeks with treatment breaks of increasing length (2, 4, 6 weeks, then 3 months). He observed no reactions to the injections other than mild redness at the injection site initially after each injection (later only at strength 10mg/mL). He also started taking a herbal remedy containing wild strawberry leaves and grape leaves (Hepatodoron®, Weleda AG, Schäbisch Gmünd, Germany), two tablets three times daily (ongoing when we last met this patient on 7th July 2014).

Colonoscopy and laboratory tests (including complete blood count, liver function tests, and CEA) were done at months 6, 12, and 24 postoperatively and were normal except for mild macrocytic anaemia. At 24 months, two small hyperplastic rectum polyps were detected and removed. He remained in good health except for a dental abscess at month 22, and had normal bowel movements without blood.

Five years postoperatively, now aged 83 years, this patient complained of psychological stress over several months due to the worsening health of his wife. Iscador® treatment breaks were therefore shortened to 4 weeks each. At routine colonoscopy that same month (Fig. 1), three budding sessile polyps were discovered on biopsy from the distal and mid-sigmoid colon as well as the transverse colon (Fig. 2A). Pathology of the mid-sigmoid polyp revealed a broad-based tubular adenoma with high-grade intraepithelial dysplasia; the pathology was performed by a private pathologist (Nurtingen, Germany). The patient cancelled the planned endoscopic resection due to the hospitalization of his wife; she died only days later. One month later he accepted a renewed colonoscopy but did not consent to resection, fearing complications. Instead, "Iscador®Qu 5mg spezial" was injected directly into the polyp.

Eight months later the patient finally agreed to colonoscopic resection. An MRI of the abdomen revealed no colon wall transgressing tumour growth, no lymph node metastases, and no focal lesions. Chest X-ray showed mild, age-related emphysema. On colonoscopy the polyp had an uneven surface and had grown, measuring now 7x4 mm and 3mm in height (Fig. 2B). Submucosal saline injection to raise the polyp revealed a non-lifting sign, indicating deeper submucosal infiltration so that endoscopic resection was not considered a viable option. 10mg Iscador®Qu was injected into the polyp and the area marked with methylene blue for later resection. No further biopsy was taken. Both intratumoural *Viscum album* injections were well tolerated.

Segmental colon resection was recommended but the patient decided against the intervention, fearing surgery could jeopardize his good general health. Nine months later, the methylene blue marked area was easily identified during colonoscopy but the polyp had now disappeared (Fig. 2C).

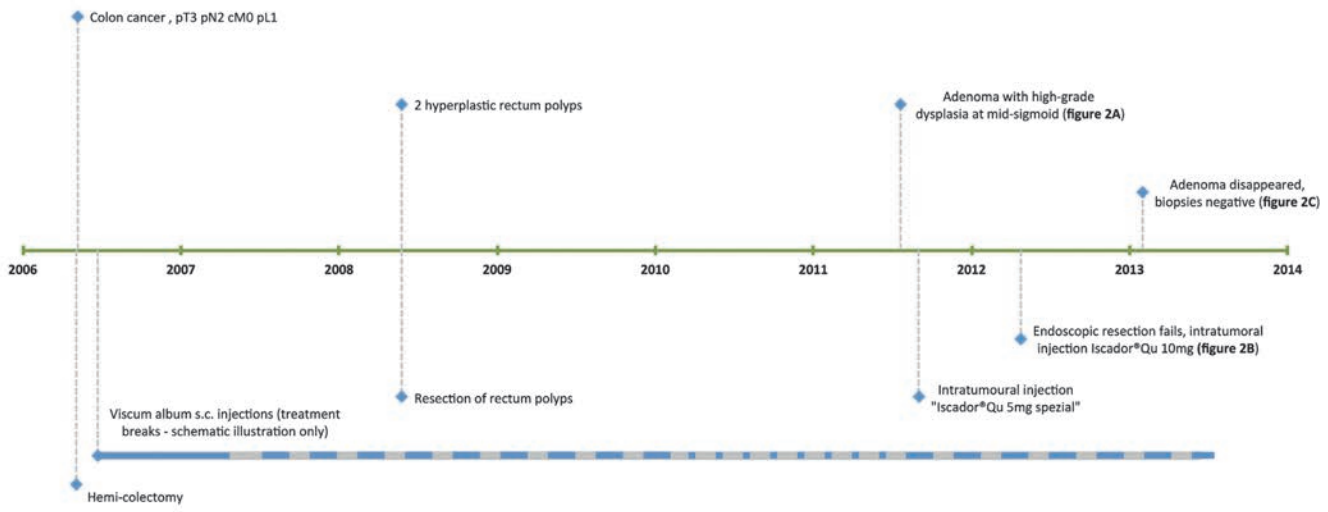

Fig. 1. Timeline of tumour events and interventions

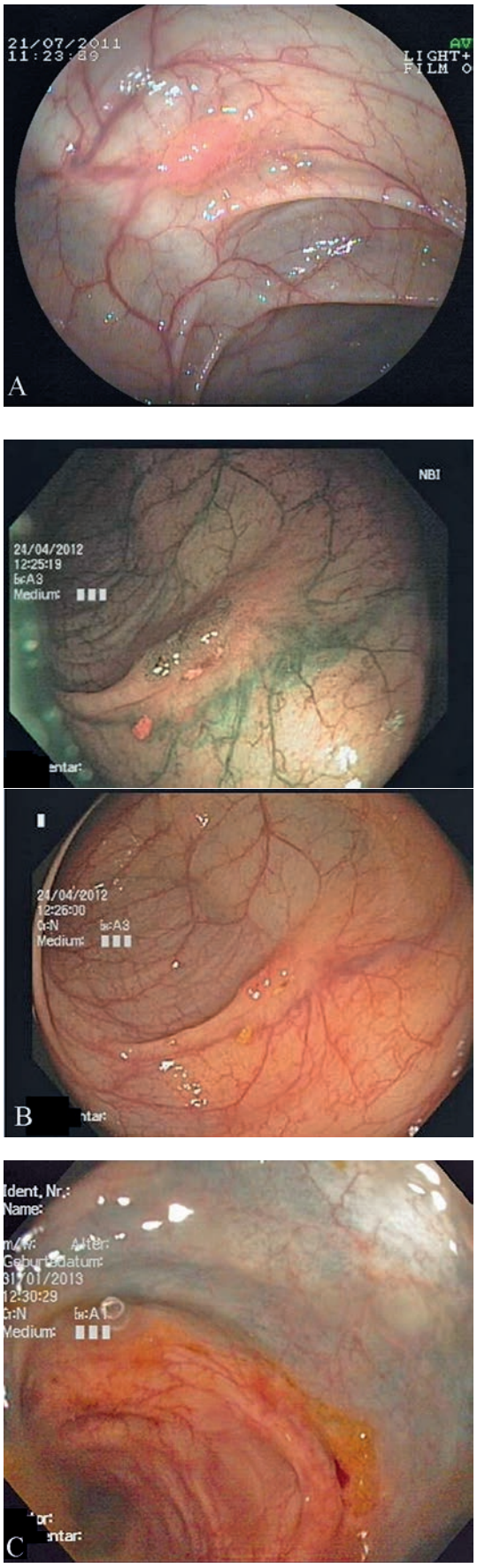

Fig. 2. A) Adenoma at first biopsy. B) Adenoma before the second intratumoural injection and labeling with methylene blue (upper image with narrow band imaging). C) Adenoma has disappeared (ink marked area).

Biopsy samples taken from the area revealed no signs of intra-epithelial dysplasia or adenoma. Patient perspective: "I believe the new tumour was a result of the stress from the illness of my wife. I decided against an operation because I did not want to risk my good health at the time. The good outcome confirmed to me that we should not blindly handover responsibility to doctors but also trust our own intuition."

The patient read the final report and gave signed informed consent for its publication. This case is reported according to CARE guidelines [16].

DISCUSSION

Following two intratumoural injections of *Viscum album* extract a complete regression of a high-grade adenomatous colon polyp was observed and confirmed by pathology. The sequence of events we have documented in this patient – culminating in the disappearance of adenoma after two intratumoural injections - indicate an effect of *Viscum album* extract treatment. Spontaneous disappearance of colon polyps sometimes occurs in patients with familial adenomatous polyposis, and spontaneous remission of an invasive colorectal cancer has previously been reported [17, 18]. However, disappearance of colon polyps is otherwise uncommon [19]. Remission of malignant tumours after intratumoural injection of *Viscum album* extracts has been reported for cutaneous B-cell lymphoma, cutaneous squamous cell carcinoma, and malignant melanoma [6-8], but not yet for colon adenomas. The effect is plausible given the known immune-stimulatory and cytotoxic effects of *Viscum album* extract [12-14].

The overall outcome in this patient, in light of his refusal of chemotherapy, was favourable: observed 5-year survival for stage IIIC colorectal cancer is only around 28% in these patients [20]. The subcutaneous *Viscum album* extract injections may have contributed to this outcome [9] but were not sufficient to prevent adenoma formation. Case reports of tumour remission after intratumoural injection suggest that concentration of the extract at the tumour site is of key importance.

Regardless of the fortunate outcome in this case, resection of colon adenoma is always advisable. Endoscopic resection can be done even for larger polyps, and the positive predictive value of a non-lifting sign for sub-mucosal invasion is only 80% [2, 21]. Other experienced practitioners may have attempted endoscopic resection in this patient.

A method to reduce polyp size could be useful in cases where an adenoma is too large for endoscopic resection and/or when the patient, after being fully informed of treatment options, does not accept the recommended therapy [22].

The safety of *Viscum album* extracts has been well documented [13]. As part of the intended immune reaction, patients typically experience some redness and swelling at the subcutaneous injection site (as in this patient) and/or low-grade fever. Anaphylactic reactions are possible, but very rare [13].

CONCLUSIONS

This is the first report showing complete regression of a colon adenoma after intratumoural injection with *Viscum*

album extract. Prospective studies should evaluate if this effect can be reproduced and if it can be a useful pre-operative method to reduce size in colon adenomas too large for endoscopic resection.

Conflicts of interests: Within the last 5 years IFAEMM (affiliation of GSK and HK) received restricted research grants from the pharmaceutical company Weleda. The company had no role at any stage in the analysis presented or in manuscript preparation.

Authors' contributions: A.G. was the treating gastroenterologist, provided patient information, and reviewed the manuscript. T.v.S.A. conceptualised the report, wrote the manuscript, and prepared the graph. G.S.K, H.K, and J.V. critically reviewed the manuscript. All authors read and approved the final manuscript.

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