

Viscum album, as alternative and bridge to palliative chemotherapy in recurrent gallbladder cancer following laparoscopic radical cholecystectomy: a case report

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A 78-year-old female patient was initially treated with laparoscopic radical cholecystectomy for gallbladder cancer (pT2aN1M0, stage IIIB). The patient then received adjuvant chemotherapy with gemcitabine. After completion of adjuvant chemotherapy, multiple lymph node metastases were observed in follow-up computed tomography (CT) scan, but the patient refused to go through further chemotherapy. One year after the recurrence, carbohydrate antigen 19-9 (CA19-9) level was 1,925 U/mL with follow-up high-resolution CT/abdomen-pelvic CT showing the increased size of multiple lymph node metastases, and the patient began to undergo *Viscum album* therapy (0.2 mg, subcutaneously, three times a week). After the *V. album* therapy was initiated, a decrease in the size of metastatic lymph nodes and CA19-9 level, which was decreased to 252 U/mL, was observed. Seventeen months after continuous *V. album* therapy, the patient agreed to have palliative chemotherapy. The patient underwent gemcitabine plus cisplatin chemotherapy and showed stable disease during follow-up. This case report suggests that *V. album* therapy showed anticancer effects and may act as a bridge to palliative chemotherapy for patients with inappropriate general conditions to undergo chemotherapy for recurrent gallbladder cancer.

Keywords: Gallbladder neoplasms, Recurrence, Drug therapy, Chemotherapy, *Viscum album*

INTRODUCTION

Gallbladder cancer is a rare cancer, accounting for 1.2% of cancer worldwide [1]. In Korea, gallbladder cancer showed an incidence rate of 2.96/100,000 (2009–2013) [2]. Despite its rare incidence, the 5-year survival rate of gallbladder cancer was 28.8% in Korea [3]. This poor outcome is thought to be due to ambiguous symptoms of

gallbladder cancer, which delay its diagnosis before it has advanced or metastasized, leading to overall progression [1]. In the case of resectable gallbladder cancer, surgical resection is the only curative treatment option, with perioperative chemotherapy [4]. For unresectable gallbladder cancer, a palliative chemotherapy regimen of gemcitabine and cisplatin is standard of care [4]. However, some patients may suffer from the adverse effects of the anticancer agents, which makes it hard for them to continue the chemotherapy.

Viscum album, also known as European mistletoe, has been used in integrative medicine to enhance the quality of life and to reduce adverse effects in cancer patients [5,6]. It has been studied that *V. album* extracts have cytotoxicity and immunomodulatory effects, which are presumed to show anticancer activity [7-9]. Effect of *V. album* has been noticed in several other cancers. Previous studies have shown that *V. album* may induce prolongation of survival time in cancer patients [10-12]. *V. album* also improves the quality of life in cancer patients and reduces the adverse effects of conventional chemotherapies [6].

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However, no previous study was done to evaluate the effect of *V. album* on gallbladder cancer. Here, we report a case of recurrent gallbladder cancer after laparoscopic radical cholecystectomy, treated with *V. album* as a bridge to subsequent palliative chemotherapy. This report was approved by the Institutional Review Board of Severance Hospital (4-2023-0907). The informed consent was waived.

CASE REPORT

A 78-year-old female patient was admitted for further evaluation and proper management of a mass in the gallbladder body. She had a history of ectopic pregnancy. There was no abnormal finding in review of systems and physical examination. She had no history of smoking and drinking. Preoperative abdomen-pelvic computed tomography (CT) showed a 2.5 cm irregular enhanced wall thickening and luminal protruding mass in gallbladder body with suspicious regional lymph node (LN) metastasis (Fig. 1A). Pancreatobiliary endoscopic ultrasound demonstrated a 33.7 mm-sized hyperechoic mass without posterior shadowing in gallbladder with invasion to perimuscular connective tissue. Mass with increased ¹⁸F-fluorodeoxyglucose (F-18 FDG) uptake in gallbladder fundus and LN with FDG uptake in right retroperitoneal space was found on positron emission tomography/CT (PET/CT) (Fig. 1B).

The patient underwent laparoscopic radical cholecystectomy on June 12, 2017. Regional LNs of hepatoduodenal ligament, common hepatic artery, and left gastric artery were dissected. Some of the liver bed was also removed, attached to gallbladder, to reduce gallbladder perforation and exposure. The safety margin was 3.5 cm in cystic duct and 1.2 cm in liver parenchyma. Intraoperative pathology

consultation was done with a frozen section of cystic duct margin, which was free from tumor. The operation took 3 hours, the estimated blood loss was 50 mL, and transfusion was not done.

The pathological examination reported that the mass was moderately differentiated adenocarcinoma of gallbladder. Tumor size was about 2.0 cm, and all resection margin was free of carcinoma. Adenocarcinoma invaded perimuscular connective tissue of peritoneal side but not serosa (pT2a). Two regional LNs out of 12 LNs dissected were found to be metastatic (pN1), and there was no sign of distant metastasis (M0). It was pathologically confirmed to be in stage IIIB (pT2aN1M0). Immunohistochemical stain showed CK19(+) on ductal glands of attached bile duct, mutation of p53 absent, HER2(2+). The patient's postoperative recovery was uneventful. She subsequently received postoperative adjuvant chemotherapy with six cycles of gemcitabine 1,000 mg 1 month after surgery. No evidence of recurrence was seen in follow-up CT during adjuvant chemotherapy. Adjuvant chemotherapy was completed on December 12, 2017.

On May 21, 2018, a follow-up CT showed the interval growth of multiple LNs in left paraaortic and left common iliac area, suggesting recurrent LN metastasis. PET/CT also demonstrated multiple LNs with increased FDG uptake along the portacaval space, paraaortic space, and bilateral common iliac chain, suggestive of metastatic LNs. The carbohydrate antigen 19-9 (CA19-9) level, which was 35.9 U/mL 4 months ago, also showed an elevation to 147 U/mL. The patient was recommended to go through chemotherapy, but she strongly refused due to severe chemotherapy-related toxicity and disappointment. As a result, the recurrent disease was shown to progress continuously.

On May 20, 2019, *V. album* subcutaneous injection therapy was

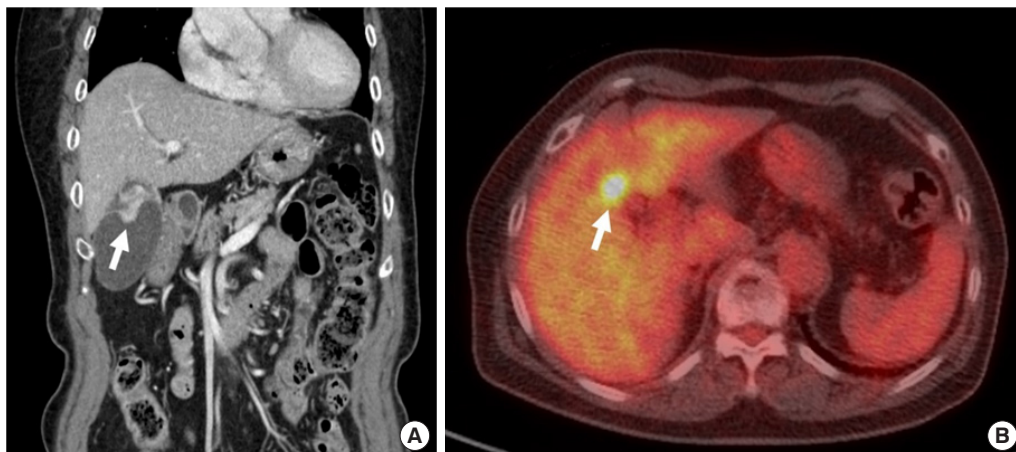


Fig. 1. Preoperative images. (A) Preoperative abdomen-pelvic computed tomography (CT) demonstrated a 2.5 cm irregular enhanced wall thickening and luminal protruding mass in gallbladder (arrow). (B) Preoperative positron emission tomography/CT (PET/CT) showed a mass with increased F-18 FDG (¹⁸F-fluorodeoxyglucose) uptake in gallbladder (arrow).

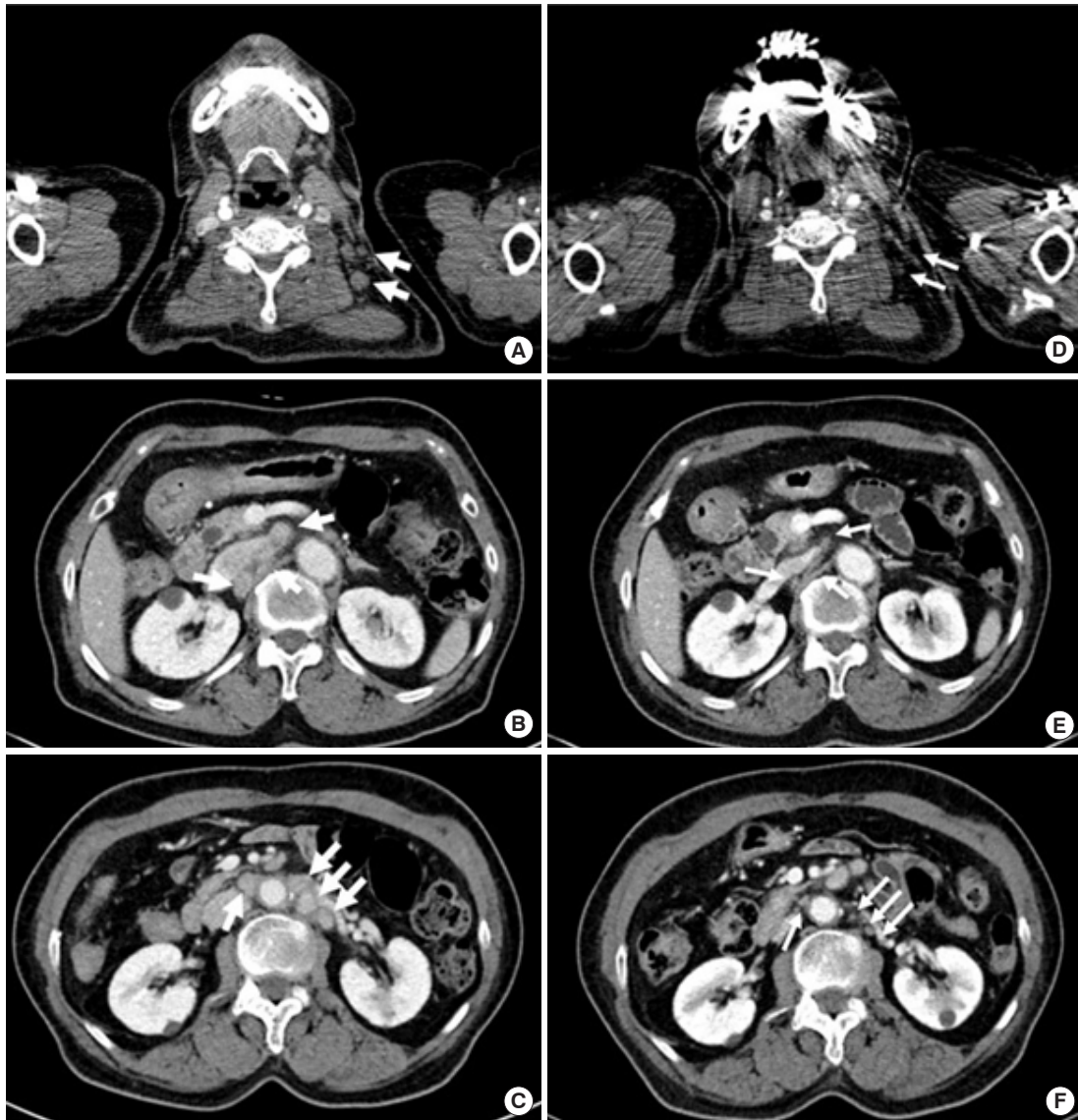


Fig. 2. The course of recurrent gallbladder cancer and treatment with *Viscum album*. (A-C) Taken on May 17, 2019. (A) HRCT for chest and neck taken before the initiation of *V. album* therapy, showed an enlarged supraclavicular fossa mass (arrows). (B) APCT taken before the initiation of the therapy, showed an enlarged portacaval mass (arrows). (C) APCT taken before the initiation of the therapy, showed an enlarged paraaortic mass (arrows). (D-F) Taken on March 17, 2020. (D) HRCT taken showed the interval decrease of supraclavicular fossa mass (arrows). (E) APCT taken showed the interval decrease of portacaval mass (arrows). (F) APCT taken showed the interval decrease of paraaortic mass (arrows). HRCT, high-resolution computed tomography; APCT, abdomen-pelvic computed tomography.

initiated instead of conventional palliative chemotherapy. Protocol of Abnovaviscum was used to decide the dosage and interval of *V. album* injection. The 0.02 mg was injected on May 20, 2019. After the initiation of the treatment, a follow-up abdomen-pelvic CT was taken on August 26, 2019, showing a gross interval decrease of multiple metastatic LNs. Abdomen-pelvic CT with contrast done on December 5, 2019, showed further decreased multiple metastatic LNs (Fig. 2). However, on November 6, the patient experienced relapsing fever and dermatitis at the injection site, which are common-

ly expected side effects of *V. album* treatment [13]. This occurred after the dosage was increased to 2 mg on October 28. After topical corticosteroid treatment and temporary discontinuation of *V. album*, dermatitis was effectively managed. The patient resumed *V. album* therapy with a reduced dose of 0.2 mg on December 2. Notably, no other side effects were reported during the remaining treatment period. CA19-9 level showed a constant and significant decrease during the period of *V. album* therapy as it decreased from 1,925 U/mL, before the initiation of therapy, to 252 U/mL after the

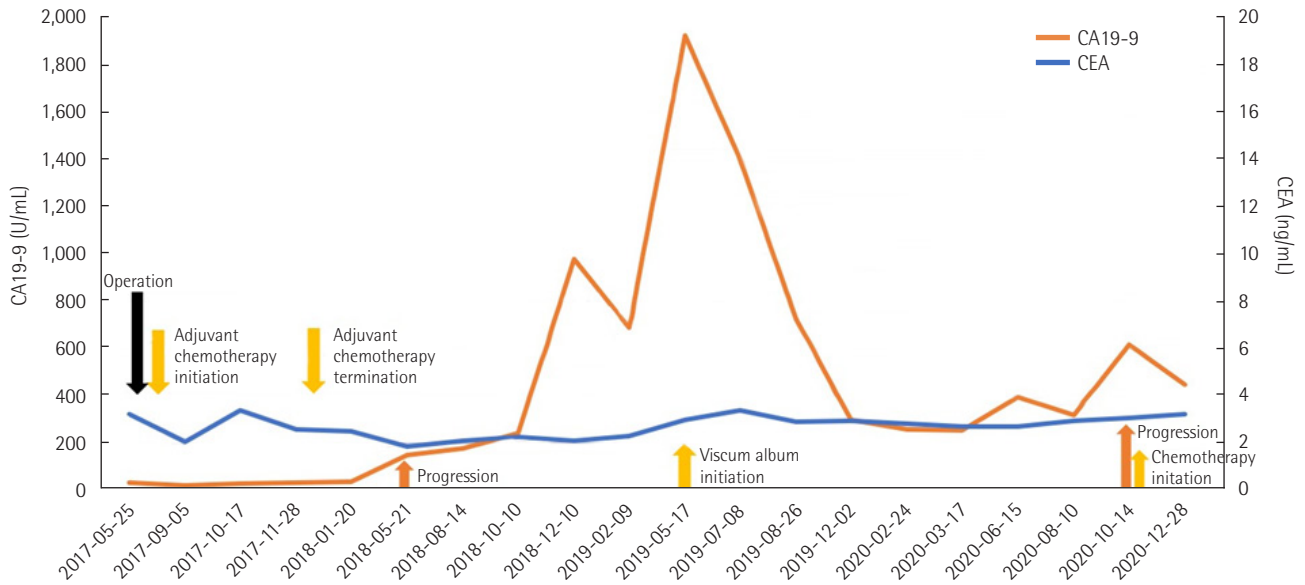


Fig. 3. Change of carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) level through the course of postoperative treatment. CA19-9 decreased rapidly as the *Viscum album* therapy was initiated. Progression occurred about 18 months after the initiation of the therapy.

therapy was done for 10 months (Fig. 3). Despite the lack of evidence, we decided to continue *V. album* therapy until the screening shows evidence of progressive disease.

V. album, as a bridge to subsequent palliative chemotherapy: Abdomen-pelvic CT taken on October 14, 2020 (about 1 and half years after *V. album* treatment/about 40 months after surgery) showed slightly increased sizes of metastatic lymphadenopathies with CA19-9 level from 317 to 617 U/mL. At this moment, the patient agreed to have second-line palliative chemotherapy, and second chemotherapy with gemcitabine plus cisplatin was initiated on October 26, 2020. Six cycles of gemcitabine plus cisplatin chemotherapy were successfully done, showing stable disease during follow-up (RECIST).

DISCUSSION

Gallbladder cancer is a rare malignancy but is the most common malignancy of the biliary tract. The diagnosis of gallbladder cancer is usually delayed due to its vague symptoms, which is the cause of its poor prognosis. Since gallbladder cancer usually advances at the time it is diagnosed, additional therapy after surgery is important in the treatment of gallbladder cancer.

Recurrent advanced gallbladder cancer is usually managed with chemotherapy. Effective regimens for chemotherapy have been established through investigations, although the current evidence is mainly established for biliary tract cancer in general, which means that there is no specific palliative chemotherapy regimen for gall-

bladder cancer [4].

Combined chemotherapy with gemcitabine and cisplatin is the first-line therapy, while there is limited evidence for the second-line regimen for chemotherapy for gallbladder cancer [4]. However, because of the adverse effects of chemotherapy, some patients may not be able to continue the treatment. In this case, it was clinically difficult to proceed with the second-line chemotherapy in principle because the patient was elderly and had already undergone the first-line chemotherapy.

In such a case, *V. album* may be an alternative choice because it is known to be a safe agent with mild adverse effects and improves the quality of life in cancer patients. In this case, *V. album* may serve as “bridge therapy,” which could modulate cancer until the patient can restart chemotherapy. There is plenty of evidence that *V. album* has anti-tumor properties, including immunomodulation and cytotoxicity, both *in vitro* and *in vivo* [7-10]. However, the oncological effects of *V. album* have not been proven in randomized controlled trials [14,15]. Pelzer et al. [14] reported that no significant differences in relapse or metastasis were found in patients who have been treated with *V. album*. Grossarth-Maticek et al. [10] reported that there was no significant effect of long-term *V. album* therapy on tumor progression. Moreover, the clinical evidence for using *V. album* for gallbladder cancer is still insufficient.

In this case, after 5 months from the adjuvant chemotherapy with gemcitabine and cisplatin, interval change of abdomen-pelvic CT and CA19-9 showed the asymptomatic recurrence of cancer. Starting chemotherapy again was recommended, but it could not

be started as the patient refused it. As an alternative therapy, a subcutaneous injection of *V. album* was used. During the therapy, follow-up abdomen-pelvic CT showed a decreasing tumor burden, and serum CA19-9 level showed a rapid and significant drop. Though the progression of cancer occurred eventually, the patient stayed progression-free and even regressed for about 17 months, gaining enough time to prepare for chemotherapy. Considering that no other anticancer agents were provided for the patients, this tumor regression phenomenon was thought to be derived from *V. album* therapy.

To the best of our knowledge, this is the first reported case of usage of *V. album* in gallbladder cancer. In this case, *V. album* showed a potential to become a decent “bridge therapy,” not only being an alternative for patients who are not able to use chemotherapy but also modulating the cancer progression until the patients are ready to go through chemotherapy. Further research is needed to investigate the clinical effect of *V. album* in gallbladder cancer.

CONFLICT OF INTEREST

This study was partly supported by Abnoba Korea research grant (4-2021-0077): oncologic impact of postoperative Abnobaviscum injection in resected pancreatic cancer. Apart from this, there were no reported conflicts of interest relevant to this article.

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