Combination of *Brucea javanica* oil emulsion and Aidi injection associated with the long-term survival of a patient with colon cancer and lung metastases post-chemotherapy: A case report

JIAJUN SONG[1*], HAILUN ZHOU[1*], CHENBING SUN[1], LIJING JIAO[1,2], YABIN GONG[1], JIALIN YAO[1] and LING XU[1,2]

[1]Department of Oncology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, P.R. China; [2]Institute of Translational Cancer Research for Integrated Chinese and Western Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, P.R. China

Received December 7, 2023; Accepted May 15, 2024

DOI: 10.3892/ol.2024.14494

Abstract. Colorectal cancer (CRC) ranks as the third most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality worldwide. Treatment options for patients with advanced CRC recurrence and metastases remain limited, particularly for those unable to withstand chemotherapy. *Bruscea javanica* oil emulsion (BJOE) and Aidi injection (ADI) are two plant-derived products that have antitumor effects. The current report presents the case of a patient with colon cancer and resectable lung metastases. Despite the surgical removal of the metastatic lesions, tumor recurrence was not prevented. The patient underwent three chemotherapy regimens following lung metastasis surgery, namely XELOX, single-agent irinotecan and single-agent tegafur-gimeracil-oteracil potassium capsule, but experienced intolerable adverse reactions with each, and disease progression was observed during subsequent follow-up. Nonetheless, the patient achieved a progression-free survival of >5 years under BJOE + ADI treatment and continues to receive BJOE + ADI treatment to date. Although further research is required to understand the effectiveness of this treatment combination, the present case may instill hope in the treatment of future patients.

Correspondence to: Professor Ling Xu or Dr Jialin Yao, Department of Oncology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, 110 Ganhe Road, Shanghai 200437, P.R. China
E-mail: xulq67@aliyun.com
E-mail: lakersbao@126.com

*Contributed equally

Key words: colorectal cancer, *Brucea javanica* oil emulsion, Aidi injection, lung metastasis, case report

Introduction

Colorectal cancer (CRC) ranks as the third most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality worldwide (1,2). Surgical resection remains the preferred treatment strategy for early-stage CRC, whilst systemic therapies, such as targeted therapies and immunotherapy, have demonstrated promising outcomes (3). Nonetheless, treatment options for patients with advanced CRC recurrence and metastases remain limited, particularly for those unable to withstand chemotherapy.

Brucea javanica oil emulsion (BJOE) is derived from a product that is extracted from the seeds of *B. javanica* and emulsified by purified soybean lecithin (4). An increasing number of studies have revealed the desirable antitumor effects of BJOE (5-7). Studies have reported that BJOE may have a regulatory role in a number of pathways, including MAPK and NF-κB signaling, the late endosomal/lysosomal adaptor and MAPK and mTOR activator 3/mTOR/autophagy related protein 13 signaling axis and the PI3K/Akt signaling pathway, as well as several other antitumor mechanisms, resulting in a wide array of antitumor effects (8-10). Moreover, BJOE is widely used in combination regimens to enhance antitumor efficacy. For example: The combination of BJOE with anti-programmed cell death protein-1 therapy has been reported to markedly inhibit the growth of melanoma (11); BJOE in combination with radiation increased the number of DNA double-strand breaks in esophageal squamous cell carcinoma cells (12); and BJOE combined with chemotherapy demonstrated an improved clinical efficacy compared with chemotherapy alone in the treatment of malignant pleural effusion (13).

Aidi injection (ADI) is a product derived from natural medicinal sources that is composed of extracts from *Mylabris phalerata*, *Astragalus membranaceus*, *Panax ginseng* and *Acanthopanax senticosus*. The clinical antitumor efficacy of Aidi injection is widely acknowledged in China, with the treatment assessed for its positive impact on cancer survival rates, tumor response, patient quality of life, and its ability to

mitigate the adverse effects of chemotherapy and radiotherapy, especially in the treatment of lung cancer, liver cancer and CRC (14). Furthermore, for patients with advanced CRC, ADI has been reported to notable reduce the risk of common chemotherapy side effects such as nausea, vomiting, diarrhea, leukopenia and thrombocytopenia (15,16). In the antitumor process, ADI promotes apoptosis and inhibits angiogenesis and cell proliferation (17-19). ADI also exhibits a protective effect on normal cells and tissues (20).

The current report presents the case of a patient with colon cancer with resectable lung metastasis that was treated with BJOE + ADI following surgical resection of the metastatic lesion.

Case report

A 69-year-old male patient presented to Fudan University Shanghai Cancer Center (Shanghai, China) in March 2015 with increased bowel movements of 2-3 times daily, which was accompanied by fresh blood and occasional abdominal pain. A colonoscopy revealed a mass of 25-30 cm from the anal verge, which occupied 75% of the circumference of the bowel lumen. Preoperative pelvic computed tomography (CT) showed no significant abnormalities (data not shown); however, abdominal magnetic resonance imaging (MRI) identified a suspicious signal in segment S7 of the liver, hepatic cysts and a slightly thickened gallbladder wall (data not shown). In addition, chest CT demonstrated a pulmonary bulla in the upper lobe and fibrotic lesions at the base of the right lung (data not shown). Consequently, the patient underwent an open left hemicolectomy in April 2015. The subsequent pathology results, performed and interpreted by professional pathologists and technicians at the Pathology Department of Fudan University Shanghai Cancer Center, indicated that the tumor, located in the transverse colon and classified as a polypoid type, measured 4.5x5.5x1.0 cm. The tumor was histologically categorized as a mucinous adenocarcinoma based on the histological examination, which adhered to the World Health Organization criteria (21). The histopathological examination was conducted as follows: The tissue samples were fixed within 30 min post-excision using a 10% neutral buffered formalin solution, with the fixative volume being 10 times that of the tissue; the fixation duration was 24 h at room temperature. Subsequently, 4-μm sections were prepared from the paraffin-embedded tissues. Prior to microscopy, the sections were stained using a standard hematoxylin and eosin (H&E) staining protocol to visualize cellular structures. The stained sections were observed under an Olympus BX51 light microscope (Olympus Corporation). An examination of 13 lymph nodes revealed no signs of metastatic cancer, with the specific counts being 0/1 for proximal tumor lymph nodes, 0/2 for distal tumor lymph nodes, 0/5 for peritumoral lymph nodes and 0/5 for mesenteric lymph nodes. The colon tumor had invaded the subserosal layer without evidence of vascular or neural invasion, and the surgical margins were free of cancer cells (data not shown). The microsatellite status was microsatellite stable (data not shown). Immunohistochemistry of the tumor tissues, performed and interpreted by professional technicians at the Pathology Department of Fudan University Shanghai Cancer Center, demonstrated p21 (+), p53 (+), CD44 (+), human epidermal growth factor receptor 2 (partially +), cyclooxygenase-2 (+), E-cadherin (+), Ki-67 (+; 70%), human mutL homolog-1 (+++), human mutS homolog (hMSH)6 (++), postmeiotic segregation increased 2 (+++), EGFR (-), B-cell lymphoma 2 (-), multi-drug resistance protein (-), topoisomerase II (+), glutathione-S-transferase π (+) and hMSH2 (+++) (data not shown). The 4-μm pathological sections were prepared as aforementioned, and immunohistochemistry was performed as follows: 0.1% Triton X-100 was used for permeabilization at room temperature for 10 min after cell fixation. The sections were then blocked with 5% BSA (cat. no. A7030; MilliporeSigma) at 4˚C overnight and were incubated with the following primary antibodies (Abcam): p21 (clone EPR362; cat. no. ab109520; dilution 1:200), p53 (clone Y5; cat. no. ab32049; dilution 1:200), CD44 (clone EPR1013Y; cat. no. ab51037; dilution 1:500), human epidermal growth factor receptor 2 (clone EP1045Y; cat. no. ab134182; dilution 1:500), cyclooxygenase-2 (clone EPR12012; cat. no. ab179800; dilution 1:500), E-cadherin (clone EP700Y; cat. no. ab40772; dilution 1:500), Ki-67 (clone SP6; cat. no. ab16667; dilution 1:300), human mutL homolog-1 (clone EPR3894; cat. no. ab92312; dilution 1:200), hMSH6 (clone EPR3945; cat. no. ab92471; dilution 1:200), postmeiotic segregation increased 2 (clone EPR3947; cat. no. ab110638; dilution 1:200), EGFR (clone EP38Y; cat. no. ab52894; dilution 1:500), B-cell lymphoma 2 (clone 100:D5; cat. no. ab692; dilution 1:200), multi-drug resistance protein (clone EPR10364-57; cat. no. ab170904; dilution 1:250), topoisomerase II (clone EPR5377; cat. no. ab109524; dilution 1:500), glutathione-S-transferase π (clone EPR4236; cat. no. ab138491; dilution 1:200) and hMSH2 (clone 3A2B8C; cat. no. ab52266; dilution 1:200). All primary antibodies were incubated at 4˚C overnight. Subsequently, the sections were incubated with secondary antibodies (1:1,000; Goat Anti-Rabbit IgG H&L, cat. no. ab205718; Goat Anti-Mouse IgG H&L, cat. no. ab6708; both from Abcam) at room temperature for 1 h. The DAB chromogenic agent was purchased form Dako; Agilent Technologies, Inc. (cat. no. K5007). The duration of DAB staining was 10 min at room temperature. The sections were detected under an Olympus BX51 microscope. Following integration of the pathological findings and immunohistochemical profile, the postoperative stage of the patient was determined to be p-T3N0M0 (Tumor-Node-Metastasis Staging System; American Joint Committee on Cancer, eighth edition) (22), corresponding to stage IIa, with proficient mismatch repair and no high-risk features identified. Based on the intraoperative findings and postoperative pathology results, the attending physicians from Fudan University Shanghai Cancer Center recommended that the patient receive adjuvant chemotherapy with 8 cycles of single-agent Xeloda® (capecitabine) to reduce the risk of cancer recurrence. Consequently, the patient received 8 cycles of chemotherapy with Xeloda (3,500 mg, orally, days 1-14, every 3 weeks) from May 2015, and subsequently received regular follow-ups.

In May 2016, during follow-up at Fudan University Shanghai Cancer Center, several nodules were found in the upper lobe of the left lung during the chest CT examination required for periodic review (data not shown). The main symptoms of the patient were fatigue, diarrhea, abnormal appetite and poor sleep quality, and a physical assessment indicated that the abdomen was palpable without any tenderness or rebound

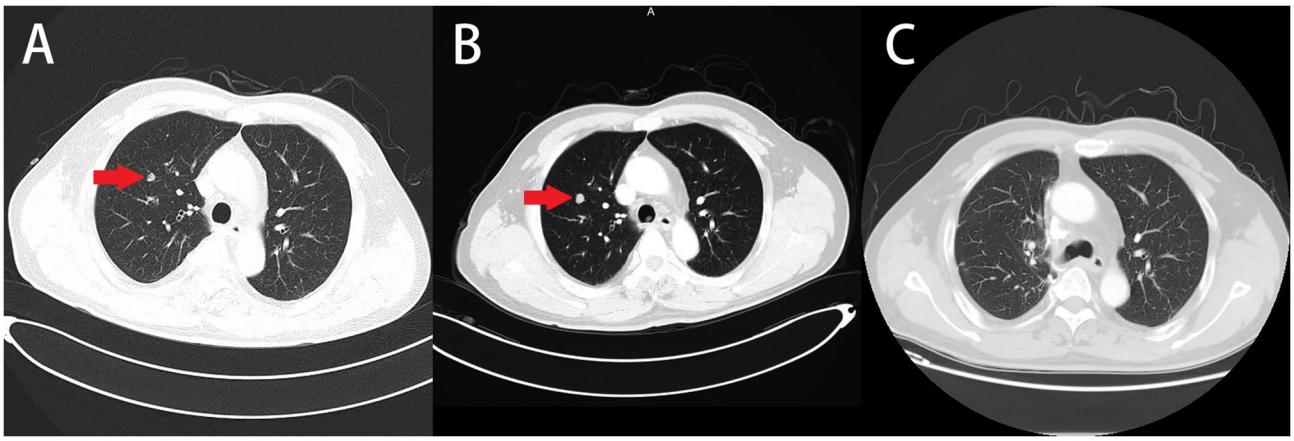

Figure 1. Comparison of chest CT before and after VATS. (A) Pulmonary window of chest CT in Aug 2016, with a visible 8-mm nodule (indicated by a red arrow). (B) Pulmonary window of chest CT in Jan 2017, with a visible 10-mm enlarged nodule (indicated by a red arrow). (C) Chest CT performed in March 2017, the nodule was removed by VATS. CT, computed tomography. CT, computed tomography; VATS, video-assisted thoracic surgery.

tenderness throughout. A well-healed 15-cm surgical scar was also observed in the lower left abdomen. In addition, there was no evidence of shifting dullness, normal bowel sounds were present, and the abdominal reflexes remained intact. The medical, family and psycho-social history of the patient contained no relevant genetic information. At this time, the patient presented to Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (Shanghai, China) for further diagnosis and treatment. Under the advice and guidance of a Traditional Chinese Medicine physician, the patient took a Chinese herbal decoction to relieve the aforementioned symptoms. A total of 3 months later, the lung nodules appeared to have progressed, with the largest nodule measuring 8-mm in diameter (Fig. 1A). At that time, the patient refused to undergo further examinations, such as positron emission tomography/CT, and opted for regular outpatient visits as follow-up instead, as there was insufficient radiological evidence to suggest pulmonary metastases. In January 2017, concerned about the potential for further enlargement of the lung nodule, the patient underwent a CT scan at Shanghai Pulmonary Hospital (Shanghai, China), which revealed a nodule in the right upper lobe of the lung, measuring 1 cm in diameter (Fig. 1B). The medical team, considering the patient's past medical history, suspected lung metastasis. After completing a thorough examination and ruling out contraindications for surgery, the patient underwent single-port video-assisted thoracic surgery for right upper lobectomy and lymphatic clearance. The postoperative pathology, performed and interpreted by professional pathologists and technicians at the Pathology Department of Shanghai Pulmonary Hospital, indicated mucinous adenocarcinoma (Fig. 2). The histopathological examination was conducted as follows: After fixation in 10% neutral formalin solution for 24 h at room temperature, dehydration was performed using absolute ethanol, followed by permeabilization with xylene at room temperature for 10 min. The samples were then embedded in regular paraffin, and 4-μm sections were cut and mounted on neutral gum-coated slides. The sections were observed under an Olympus BX51 microscope. Immunohistochemical staining revealed cytokeratin

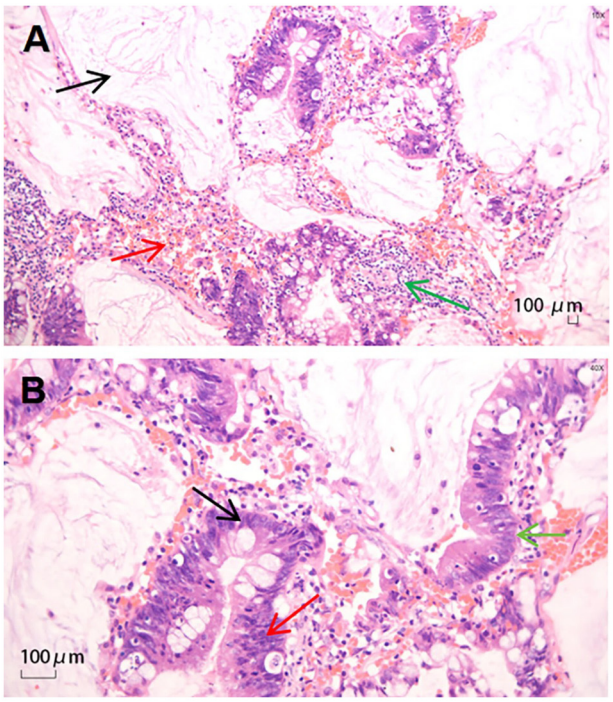

Figure 2. Microscopic images of hematoxylin and eosin staining. (A) Nests of adenocarcinoma cells were floating in the mucus (indicated by black arrow), some tumor cells were stained by eosin in the cytoplasm (indicated by red arrow), and inflammatory cell infiltration could be seen around the cancer nests (indicated by green arrowheads). (B) Nuclei of the cancer cells were cup shaped (indicated by black arrow), column shaped (indicated by red arrow) or ovoid shaped (indicated by green arrow), with nucleoli visible, and most of them were located in the basal part of the mucinous adenocarcinoma glandular cells.

(CK)5/6 (-), CK7 (+), CK20 (+), thyroid transcription factor-1 (-), p40 (-), CDK-2 (partially +) and Villin (+). The sections were prepared as aforementioned for immunohistochemistry, and the following antibodies (Abcam) were used: CK5 (clone EP1601Y; cat. no. ab52635; dilution 1:200), CK6 (clone EPR1602Y; cat. no. ab93279; dilution 1:200), CK7 (clone EPR17078; cat. no. ab181598; dilution 1:500), CK20 (clone

Table I. Treatment details.

Treatment date	Cycle	Treatment	Clinical outcome	Adverse event
2015/5-2015/12	1st-8th	Xeloda (3,500 mg, orally, days 1-14, q3w) (adjuvant chemotherapy[a])	-	-
2017/2	1st	Oxaliplatin (230 mg, ivgtt, d1) + capecitabine (3,500 mg, po, d1-14, q3w)	-	ALT increased, grade III[b]
2017/3	1st	Irinotecan (550 mg, ivgtt, d1, q3w)	-	Neutrophil count decreased, grade IV
2017/4	1st	S-1 (100 mg, po, d1-14, q3w)	-	-
2017/5	2nd	S-1 (100 mg, po, d1-14, q3w)	-	-
2017/6	3rd	S-1 (100 mg, po, d1-14, q3w)	-	Platelet count decreased, grade II
2017/6	4th	S-1 (100 mg, po, d1-14, q3w)	-	Platelet count decreased, grade II
2017/7	5th	S-1 (100 mg, po, d1-14, q3w)	2017/8 CT: SD	Platelet count decreased, grade III
2018/9	1st	30 ml BJOE + 80 ml ADI (ivgtt, d1-d8, q4w)	2018/9 CT: PD (baseline)	-
2018/10	2nd	30 ml BJOE + 80 ml ADI (ivgtt, d1-d8, q4w)	-	-
2018/11	3rd	30 ml BJOE + 80 ml ADI (ivgtt, d1-d8, q4w)	2018/12 CT: PR	-

[a]Adjuvant tegafur-gimeracil-oteracil. [b]Common Terminology Criteria for Adverse Events Version 4.03., 2010. BJOE, *Brucea javanica* oil emulsion; ADI, Aidi injection; ALT, alanine transferase; CT, computed tomography; d, day; q3w, every 3 weeks; q4w, every 4 weeks; po, orally; ivgtt, intravenous drip; SD, stable disease; PD, progressive disease; PR, partial response.

EPR1622Y; cat. no. ab76126; dilution 1:500), thyroid transcription factor-1 (clone EP1584Y; cat. no. ab76013; dilution 1:500), p40 (clone EP2142Y; cat. no. ab76158; dilution 1:200), CDX-2 (clone SP54; cat. no. ab101532; dilution 1:200) and Villin (clone SP145; cat. no. ab130751; dilution 1:200). All primary antibodies were incubated at 4˚C overnight. Secondary antibody (goat anti-rabbit IgG H&L; cat. no. ab182016; dilution 1:1,000; goat anti-rabbit IgG H&L HPR; cat. no. Ab205718; dilution 1:1,000) incubation, DAB staining and microscopy were performed as aforementioned for immunohistochemistry. Positive staining for CK7 and CK20 confirmed the presence of adenocarcinoma, whilst partial positivity for CDK-2 suggested a potential gastrointestinal origin (data not shown). Together with the patient's history and enzyme markers, this supported the diagnosis of pulmonary metastasis from colon cancer. At a follow-up in March 2017, it was confirmed that the nodule had been removed by chest CT scan (Fig. 1C).

Subsequently, the patient received another round of treatment: One cycle of XELOX [230 mg oxaliplatin, intravenous drip, day 1 + 3,500 mg capecitabine, orally, days 1-14, every 3 weeks] in February 2017. However, the patient subsequently developed severe abdominal pain and experienced an impaired grade I alanine transaminase status, with an alanine transferase (ALT) level of 292 U/l (normal range, 7-40 U/l) (23). Although the liver function returned to normal (ALT, 37 U/l; tested in March 2017) and the abdominal pain was relieved following treatment with an injection of 200 mg magnesium isoglycyrate + 1.8 g reduced glutathione (intravenous drip, days 1-10), the patient refused the original treatment plan due to concerns regarding adverse reactions. Subsequently, the regimen was adjusted to 550 mg irinotecan in March 2017 (intravenous drip, day 1, every 3 weeks). However, the patient experienced a grade IV neutrophil count decrease ($0.1x10^9$/l; normal range, $1.8\text{-}6.3x10^9$/l) following this regimen. Therefore, a 100 mg tegafur-gimeracil-oteracil potassium capsule (orally, days 1-14, every 3 weeks) for four cycles of chemotherapy (April-July 2017) was administered. However, during cycles 3 and 4, the patient developed myelosuppression again and showed a deteriorating trend with a persistent decrease in platelet count to $36x10^9$/l (normal range, $125\text{-}350x10^9$/l); thus, the chemotherapy program was suspended. The patient was requested to attend regular follow-ups.

In September 2018, a new nodule in the dorsal segment of the lower lobe of the right lung was observed by chest CT scan (Fig. 3A). Due to the distant metastases and intolerance to chemotherapy, the patient appeared to be nearing termination of treatment. However, to prolong the survival of the patient as much as possible, a 3-cycle BJOE + ADI treatment (30 ml BJOE + 80 ml ADI, intravenous drip, on days 1-8, every 4 weeks) was administered, which has been reported to have an antitumor effect and few adverse reactions. This combination is widely used in clinical practice and has demonstrated promising application value (24). In the subsequent review period (December 2018), an unexpected decrease in the nodule size was observed (Fig. 3B).

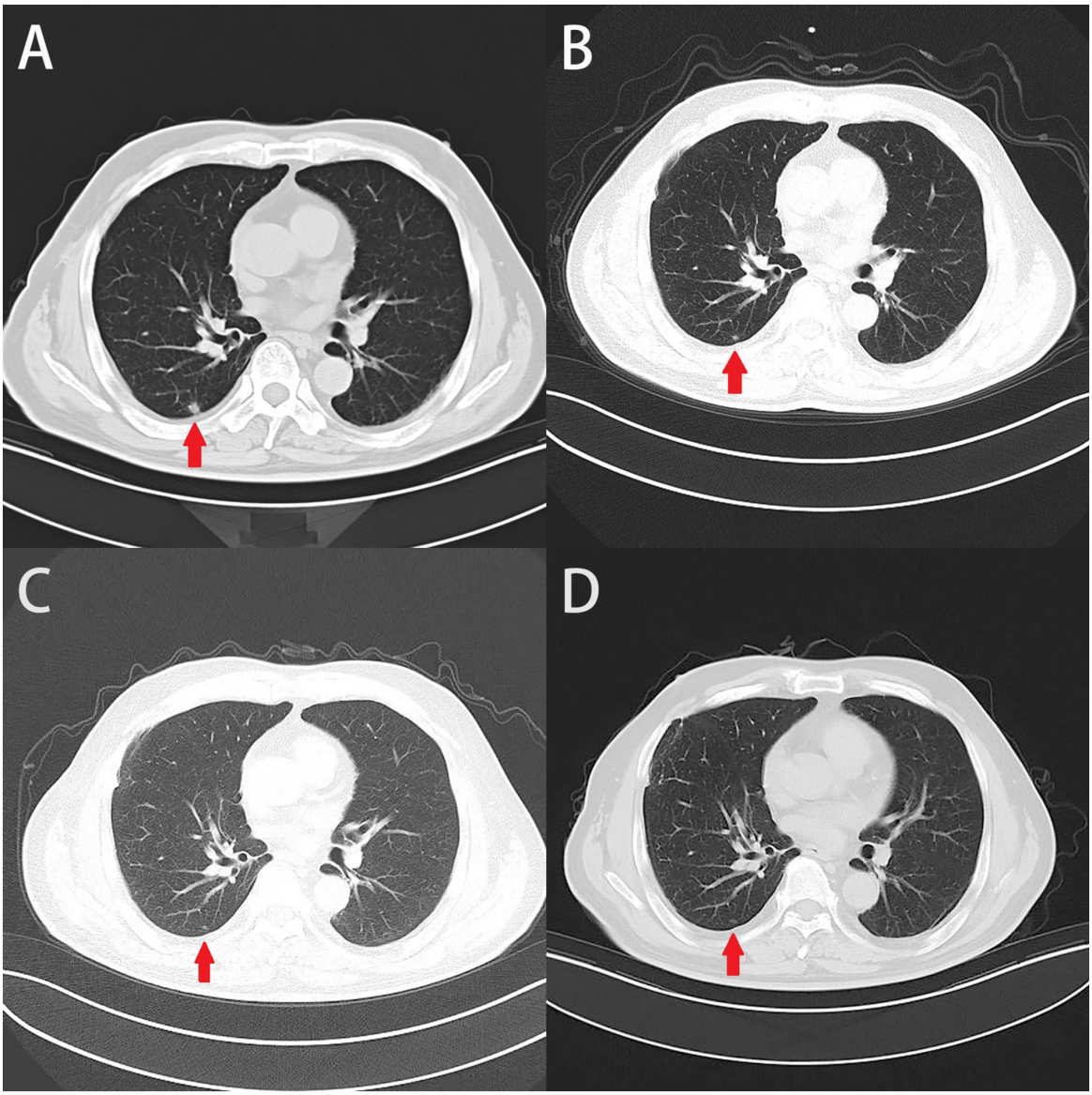

Figure 3. CT images of subsequent follow-up visits revealed the shrinkage of the nodule. (A) Pulmonary window of the chest CT performed in September 2018, demonstrating a new nodule in the dorsal segment of the lower lobe of the right lung (indicated by red arrow). (B) Chest CT performed in December 2018, after the administration of *Brucea javanica* oil emulsion + Aidi injection, in which the nodule appears to be reduced in size (indicated by red arrow). Chest CT in (C) February 2020 and (D) October 2023, demonstrating the disappearance of the nodule (indicated by red arrows) and no tumor progression. CT, computed tomography.

The treatment regimen of the patient, including the timing, medication, dosage and administration of therapies, is presented in Table I. A chest CT was performed every 3 months to monitor the changes in lung lesions, an abdominal CT or MRI was performed every 3 months and a colonoscopy was performed every 12 months to follow-up the abdominal condition of the patient. During regular follow-up, no tumor progression was observed (Fig. 3C and D).

CT in the present case was performed using the following parameters: A slice thickness of 5 mm, a reconstruction interval of 1.25 mm and exposure parameters set with a tube voltage of 120 kVp, employing automatic current modulation for broad-beam exposure. Consistency was maintained across all follow-ups by using the same CT machine and medical team for scan collection. The liver and kidney function of the patient was assessed before and after the BJOE + ADI intervention, as well as other clinical indicators such as routine blood (leukocyte, neutrophil, platelet and hemoglobin) and tumor markers (Table II). However, the results indicated that there were no significant changes in the liver and kidney function, and no notable adverse reactions were observed. The treatment history is shown in Fig. 4, and it is revealed that, from the first injection of BJOE + ADI in 2018 until the present day, the patient has >5 years of progression-free survival (PFS), which is uncommon for a patient with distant metastases and intolerance to chemotherapy, as the overall 5-year survival rate for stage IV CRC is ~15.1% (25).

Discussion

The advanced stage of CRC often poses significant challenges for achieving effective control of metastasis and

Table II. Clinical indicators of the patient during the treatment of BJOE + ADI.

Indicator	Normal range	2018/9	2018/11	2018/12	2019/1	2019/2	2019/3	2019/7	2019/11
CEA, ng/ml	≤5	6.30	5.20	4.90	2.20	2.60	2.70	2.50	2.70
CA 19-9, U/ml	≤30	29.4	26.3	22.5	20.6	30.8	25.2	29.5	30.7
WBCs, x10^9/l	3.5-9.5	5.8	4.9	4.5	7.1	5.1	5.2	8.1	4.5
PLTs, x10^9/l	125-350	121	111	123	119	108	112	135	125
ALT, U/l	9-52	17	22	25	19	25	13	12	22
Cr, μmol/l	46-92	75	88	82	85	78	82	83	84

BJOE, *Brucea javanica* oil emulsion; ADI, Aidi injection; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; WBC, white blood cell; PLT, platelet; ALT, alanine transferase; Cr, creatinine clearance.

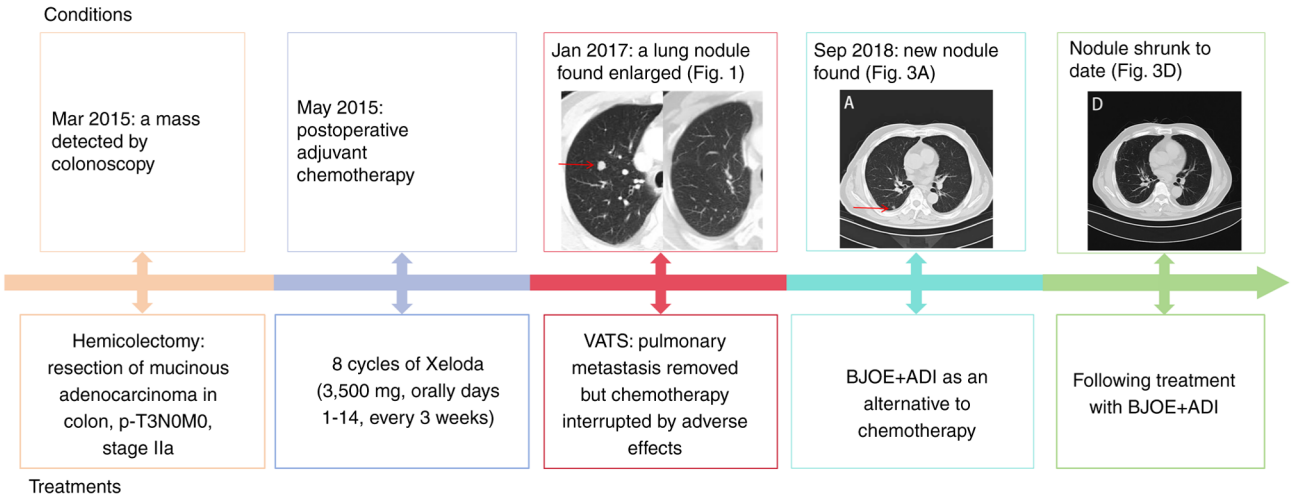

Figure 4. Overview of the medical history of the patient and the treatment programs. VATS, video-assisted thoracic surgery; BJOE, *Brucea javanica* oil emulsion; ADI, Aidi injection.

progression, which causes a mortality rate that is hard to mitigate. Furthermore, when distant metastases develop, patients are typically faced with a poor prognosis (26). Compounding the issue, the patient described in the present study was unable to tolerate chemotherapy. During the development of the treatment plan, the healthcare team underwent significant deliberation and encountered moments of uncertainty; however, through persistent communication and careful consideration of alternative options, the medical team was able to offer the patient a combination of two traditional Chinese medicinal products. The subsequent response of the patient to this treatment was encouraging, highlighting the potential of these therapies in prolonging the survival of patients with advanced CRC. Nevertheless, it should be acknowledged that chemotherapy remains the mainstay of CRC treatment, particularly for advanced and metastatic cases. However, certain patients may not tolerate chemotherapy well, or may develop resistance or recurrence following chemotherapy (27). In the present case, BJOE + ADI was used as an alternative to chemotherapy as the patient could not tolerate chemotherapy and developed a new pulmonary nodule following resection surgery. Whilst it is not suggested that this combination treatment could replace chemotherapy for all patients with CRC, it may provide a possible option for those who cannot benefit from chemotherapy.

To contextualize the findings of the present study, the existing literature was reviewed for similar cases. Several reports have documented a prolonged PFS in patients with advanced cancer using complementary and alternative therapies (28). A meta-analysis of 52 studies reported that ADI, when used as an adjunctive therapy in combination with modern medicine, may have a complementary beneficial role in improving survival time, tumor response and quality of life, and reducing the side effects of chemoradiotherapy. The most commonly studied types of cancer were lung cancer, liver cancer and CRC (14). By summarizing these studies, the understanding of the potential benefits and limitations of such treatment can be improved. Additionally, a comparative analysis with other cases would provide valuable insights into the efficacy and safety profiles of these herbal products.

The antitumor mechanisms of BJOE and ADI remain speculative; however, based on the available evidence, we hypothesize the following: Both BJOE and ADI may have enhanced the immune response of the patient. BJOE contains active compounds that stimulate natural killer cells and promote cytokine production. In addition, ADI has been associated with increased T-cell activation and improved tumor

surveillance (29). It was also been reported that the combination of bruceitol and cisplatin may enhance the antitumor effect of cisplatin and induce apoptosis of CT-26 colon cancer cells (30). Furthermore, a previous study screened the optimal compound formulation of ADI (covalent-organic framework: Composed of cantharidin, calyptoflavone-7-O-β-D-glucoside, ginsenoside Rc and ginsenoside Rd; molar ratio, 1:12:12:8). It was reported that this formulation exhibited a marked synergistic effect, leading to the inhibition of cancer cell viability, increased cell death and induction of apoptosis in nude mice models with liver cancer and CRC. Additionally, the formulation reduced mitochondrial membrane potential levels, promoted cytochrome c leakage and reduced tumor volume and weight (31).

In clinical practice, BJOE or ADI are often used as an alternative to chemotherapeutic agents in certain patients who cannot tolerate chemotherapy. These drugs exhibit a potent inhibitory effect on tumors, leading to prolonged stable disease in patients (14,28). Notably, the patient described in the present study attained an extended period of PFS following the use of this drug combination. This was an unexpected outcome that serves as a reminder of the importance of re-evaluating the antitumor potential of Chinese medicine, particularly when considering its safety profile. Nonetheless, the present case report does have limitations, such as the lack of molecular biomarkers; however, the present case report provides valuable evidence for the potential benefits of administering BJOE and ADI in patients with CRC with lung metastases. Further studies that investigate the intricate antitumor mechanisms underlying this drug combination are required, to potentially offer new therapeutic options and renewed hope for patients with advanced cancer who cannot tolerate chemotherapy.

Acknowledgements

Not applicable.

Funding

The present work was supported by the High Level of Peak Plateau (Shanghai Municipal Education Commerce, grant no. KY110.01.400), the Shanghai Frontiers Science Center of Disease and Syndrome Biology of Inflammatory Cancer Transformation (grant no. 2021KJ03-12), the Shanghai Sailing Program (grant no. 21YF1448200), the National Natural Science Foundation of China (grant no. 82305333) and the Shanghai 2022 'Science and Technology Innovation Action Plan' medical innovation research project (grant no. 22Y31920103).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JS and HZ took the lead in writing the original draft of the manuscript. JS, HZ and CS contributed to data curation and charted the course of the disease by dedicating their efforts to data collection and the case study. JS, LJ and YG participated in the discussion and analysis of the case, contributing to charting the course of the disease. JY and LX were responsible for the conceptualization of the research and the development of the methodology. JY and LX confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present case report was approved by The Ethics Committee of Yueyang Hospital (Shanghai, China; approval no. 2023-150).

Patient consent for publication

The patient provided written informed consent to publish the present case report, including the publication of images.

Competing interests

The authors declare that they have no competing interests.

References

1. Li N, Lu B, Luo C, Cai J, Lu M, Zhang Y, Chen H and Dai M: Incidence, mortality, survival, risk factor and screening of colorectal cancer: A comparison among China, Europe, and northern America. Cancer Lett 522: 255-268, 2021.
2. Sharma R, Abbasi-Kangevari M, Abd-Rabu R, Abidi H, Abu-Gharbieh E, Acuna JM, Adhikar S, Advan SM, Sohail Afzal M, Meybodi MA, *et al*: Global, regional, and national burden of colorectal cancer and its risk factors, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet Gastroenterol Hepatol 7: 627-647, 2022.
3. Ruff SM, Brown ZJ and Pawlik TM: A review of targeted therapy and immune checkpoint inhibitors for metastatic colorectal cancer. Surg Oncol 51: 101993, 2023.
4. Fuhong D, Xiang G, Haiying L, Jiangye W, Xueming G and Wenxiao C: Evaluation of efficacy and safety for *Brucea javanica* oil emulsion in the control of the malignant pleural effusions via thoracic perfusion. BMC Cancer 18: 411, 2018.
5. Wang X, Wang H, Cao L, Wu J, Lu T, Li S and Li J: Efficacy and safety of *Brucea Javanica* oil emulsion injection in the treatment of gastric cancer: A systematic review and meta-analysis. Front Nutr 8: 784164, 2021.
6. Chen J, Chen S, Yang X, Wang S and Wu W: Efficacy and safety of *Brucea javanica* oil emulsion injection as adjuvant therapy for cancer: An overview of systematic reviews and meta-analyses. Phytomedicine 102: 154141, 2022.
7. Zhou H, Wang Q, Jiao L, Bi L, Sang S, Han Y, Gan S, Liu R, A G and Gong Y: Intrapleural injection of *Brucea javanica* oil emulsion provided a long-term benefits in patient with malignant pleural effusion from pleural mesothelioma: A case report. Explore (NY) 20: 126-129, 2024.
8. Ye L, Zhao JF, Wang YM, Chen WH, Qian S, Zhou ZG and Xu M: *Brucea javanica* oil emulsion suppresses tumor growth in human cervical cancer cells through inhibition of the E6 oncogene and induction of apoptosis. Transl Cancer Res 9: 918-929, 2020.
9. Wang Y, Chen B, Xiao M, Wang X and Peng Y: *Brucea javanica* oil emulsion promotes autophagy in ovarian cancer cells through the miR-8485/LAMTOR3/mTOR/ATG13 signaling axis. Front Pharmacol 13: 935155, 2022.
10. Zhang H, Yin SL, Wang LH, Jia LN, Su GY, Liu XQ, Zhou F, Breslin P, Meng R, Li QY, *et al*: Seed oil of *Brucea javanica* induces apoptosis through the PI3K/Akt signaling pathway in acute lymphocytic leukemia Jurkat cells. Chin J Nat Med 19: 608-620, 2021.
11. Meng J, Yu Z, Chen H, Yu X, Jiang M, Zeng XA and You J: *Brucea javanica* oil emulsion significantly improved the effect of anti-programmed cell death protein-1 immunotherapy. Phytomedicine 107: 154446, 2022.

12. Pan P, Yang BX and Ge XL: *Brucea javanica* seed oil enhances the radiosensitivity of esophageal cancer by inhibiting hypoxia-inducible factor 1α, in vitro and in vivo. Oncol Lett 15: 3870-3875, 2018.
13. Shi R, Wu Z, Wang H, Zhang J, Zhang F, Stalin A, Chen M, Huang J, Zhai Y, Zhang Q, *et al*: Investigation on the efficiency of *Brucea javanica* oil emulsion injection with chemotherapy for treating malignant pleural effusion: A meta-analysis of randomized controlled trials. Front Pharmacol 13: 998218, 2022.
14. Yang M, Shen C, Zhu SJ, Zhang Y, Jiang HL, Bao YD, Yang GY and Liu JP: Chinese patent medicine Aidi injection for cancer care: An overview of systematic reviews and meta-analyses. J Ethnopharmacol 282: 114656, 2022.
15. Wang T, Nan H, Zhang C, Wang Y, Zhang X, Li Y and Mulati: Aidi injection combined with FOLFOX4 chemotherapy regimen in the treatment of advanced colorectal carcinoma. J Can Res Ther 10: 52, 2014.
16. Xie G, Cui Z, Peng K, Zhou X, Xia Q and Xu D: Aidi injection, a traditional Chinese medicine injection, could be used as an adjuvant drug to improve quality of life of cancer patients receiving chemotherapy: A propensity score matching analysis. Integr Cancer Ther 18: 153473541881079, 2019.
17. Lu Y, Zhang S, Zhu X, Wang K, He Y, Liu C, Sun J, Pan J, Zheng L, Liu W, *et al*: Aidi injection enhances the anti-tumor impact of doxorubicin in H22 tumor-containing mice. J Ethnopharmacol 303: 115968, 2023.
18. Lan HY, An P, Liu QP, Chen YY, Yu YY, Luan X, Tang JY and Zhang H: Aidi injection induces apoptosis of hepatocellular carcinoma cells through the mitochondrial pathway. J Ethnopharmacol 274: 114073, 2021.
19. Zhang W, Peng W, Li Y, Pan T, Feng F, Xu J and Zhou X: Network pharmacology and molecular docking analysis on molecular targets and mechanisms of aidi injection treating of nonsmall cell lung cancer. Evid Based Complement Alternat Med 2022: 8350218, 2022.
20. Lu Y, Liu W, Lv T, Wang Y, Liu T, Chen Y, Jin Y, Huang J, Zheng L, Huang Y, *et al*: Aidi injection reduces doxorubicin-induced cardiotoxicity by inhibiting carbonyl reductase 1 expression. Pharm Biol 60: 1616-1624, 2022.
21. WHO Classification of Tumours: Digestive System Tumours. Vol 1. 5th edition. International Agency for Research on Cancer, Lyon, 2019.
22. American Joint Committee on Cancer: AJCC Cancer Staging Manual. 8th edition. Springer, New York, NY, 2017.
23. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, 2010.
24. Gao W and Zhang K: Network meta-analysis of 8 types of traditional Chinese medicine injection combined with chemotherapy in colorectal cancer treatment. J Cancer Res Clin Oncol 149: 9823-9838, 2023.
25. Hernandez Dominguez O, Yilmaz S and Steele SR: Stage IV colorectal cancer management and treatment. J Clin Med 12: 2072, 2023.
26. Siegel RL, Wagle NS, Cercek A, Smith RA and Jemal A: Colorectal cancer statistics, 2023. CA A Cancer J Clin 73: 233-254, 2023.
27. Fu AZ, Graves KD, Jensen RE, Marshall JL, Formoso M and Potosky AL: Patient preference and decision-making for initiating metastatic colorectal cancer medical treatment. J Cancer Res Clin Oncol 142: 699-706, 2016.
28. Jazieh AR, Abuelgasim KA, Ardah HI, Alkaiyat M and Da'ar OB: The trends of complementary alternative medicine use among cancer patients. BMC Complement Med Ther 21: 167, 2021.
29. Chen HM, Lai ZQ, Liao HJ, Xie JH, Xian YF, Chen YL, Ip SP, Lin ZX and Su ZR: Synergistic antitumor effect of brusatol combined with cisplatin on colorectal cancer cells. Int J Mol Med 41: 1447-1454, 2018.
30. Lee SM, Choi HC and Hyun MK: An overview of systematic reviews: Complementary therapies for cancer patients. Integr Cancer Ther 18: 1534735419890029, 2019.
31. An P, Lu D, Zhang L, Lan H, Yang H, Ge G, Liu W, Shen W, Ding X, Tang D, *et al*: Synergistic antitumor effects of compound-composed optimal formula from Aidi injection on hepatocellular carcinoma and colorectal cancer. Phytomedicine 103: 154231, 2022.