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Case Report

Novel Use of Bromelain and Acetylcysteine (BromAc®) for Pleural Involvement in Pseudomyxoma Peritonei

Anthony R. Lam[a] Khalil Bazzi[a] Sarah J. Valle[a] David L. Morris[a, b]

[a]Department of Surgery, Peritonectomy Unit, St George Hospital, Kogarah, NSW, Australia;
[b]University of New South Wales, St George Hospital Clinical School, Sydney, NSW, Australia

Keywords
Bromelain · Acetylcysteine · Pseudomyxoma peritonei · Pleural adenomucinosis

Abstract
Pseudomyxoma peritonei (PMP) is a rare mucinous disease most commonly arising from the appendix. Pleural involvement arising from established PMP is seen in a small number of cases. Combined cytoreductive surgery and hyperthermic intrathoracic chemotherapy is the treatment of choice when managing intra-thoracic PMP. In cases of recurrence, surgical intervention may be technically challenging and carry higher rates of complications, morbidity, and mortality. Bromelain and acetylcysteine (BromAc®) is a novel treatment modality that has demonstrated mucolytic properties. When injected directly into mucinous disease, it facilitates tumour dissolution and allows it to be aspirated. It has recently been tested in the treatment of inoperable peritoneal mucinous disease, with an acceptable safety profile and positive objective response. Here we describe the first two cases of BromAc® administered directly into pleural adenomucinosis, with striking differences in response between the two patients likely due to differences in tumour hardness.

Introduction

Pseudomyxoma peritonei (PMP) is a rare mucin-producing tumour that deposits gelatinous material and spreads throughout the peritoneal cavity. PMP has an incidence of 1–3 cases per million with pleural involvement seen in only 5% of patients, which is most commonly the result of diaphragm invasion or entering the pleural space during cytore-

Correspondence to:
Anthony R. Lam, Anthony.lam1@health.nsw.gov.au

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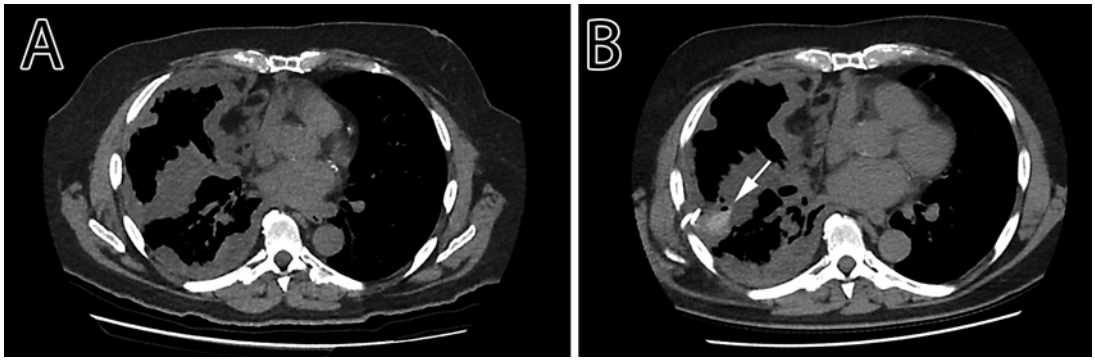

Fig. 1. Pre-treatment (**A**) axial computed tomography section demonstrating pleural recurrence from PMP disease in a 68-year-old male. **B** Day 3 post-BromAc® treatment progress scan with contrast injected through self-retaining drain. The arrow indicates only regional diffusion of contrast around the drain site.

ductive surgery (CRS) [1–3]. If untreated, progressive mucin production will exert increasing pressure on critical intrathoracic structures leading to worsening symptom burden [4].

The combination of CRS with intraperitoneal chemotherapy (IPC) now offers a significant long-term survival benefit for patients with peritoneal disease; however, this requires careful patient selection for suitability [5, 6]. Research into less invasive options may aid in managing patients who are not suitable for surgery, particularly those with recurrent disease. The synergistic effects of bromelain and acetylcysteine (BromAc®) have been investigated in in vitro and in vivo formulation studies and recently in a Phase I trial for inoperable peritoneal mucinous disease, with positive results and an acceptable safety profile [7, 8]. Bromelain is a pineapple stem extract that offers certain anti-cancer properties such as interfering with malignant cell growth and other anti-inflammatory effects [9]. It is of interest in mucin producing tumours due to its proteolytic effects [10]. Acetylcysteine is a protein well known for its use in paracetamol toxicity, although here it is of interest as it demonstrates biochemical properties that promote mucolysis with efficacy in mucin-producing diseases [11, 12]. Together, BromAc® breaks glycosidic linkages and disulfide bonds, the framework of mucin [7]. We describe the first case results of BromAc® directly injected into intrathoracic PMP via radiologically guided drains.

Case Presentation

Case 1

A 68-year-old male with PMP diagnosed and treated with peritonectomy and heated intraperitoneal chemotherapy in 2017 presented to the peritonectomy outpatient clinic as part of routine follow-up and surveillance. A computed tomography (CT) scan was performed, demonstrating evidence of extensive pleural recurrence involving the right thorax (Fig. 1A). Two radiologically guided attempts were required to insert a drain into the tumour (10-Fr self-retaining drain), due to the hardness of the tumour. Initial dose of BromAc® (30 mg/1 g in 15 mL of 5% glucose) injected via the drain directly into the tumour was tolerated well. However, subsequent daily doses over the following 2 days were poorly tolerated by the patient with the primary adverse effect being pain. Approximately 3 mL of mucinous material was aspirated 24 h after each administration despite injecting 10–20 mL of the BromAc® formulation. No immediate respiratory symptoms, fevers or anaphylaxis were observed. A

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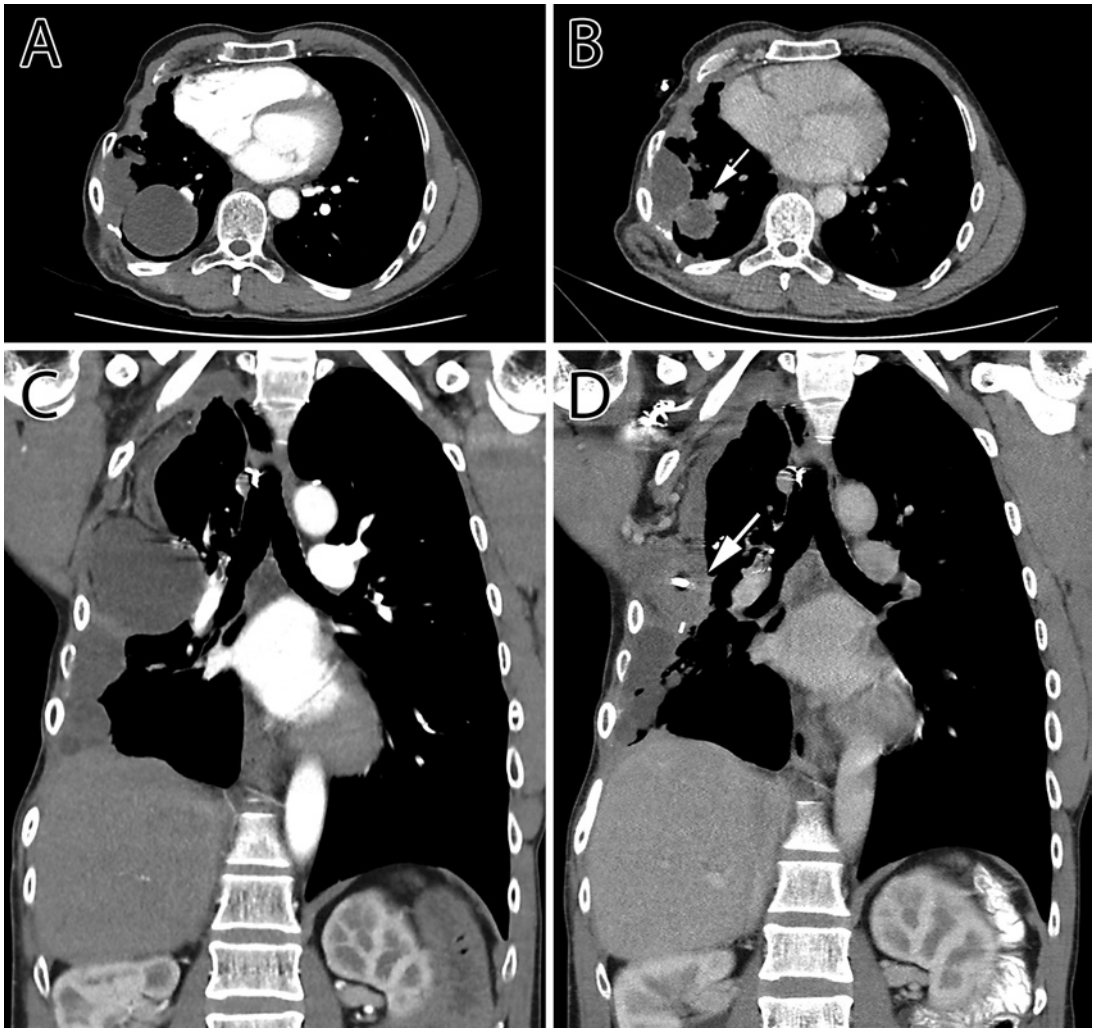

Fig. 2. Pre-treatment (**A**, **C**) computed tomography sections of significant loculated pleural recurrence from PMP disease in a 41-year-old male. Day 16 (**B**, **D**) post-BromAc® treatment progress images demonstrating reduction in size of previous mucinous mass as indicated by the white arrows.

progress CT scan was performed after the third and final dose with contrast injected through the drain illustrating only local penetration of contrast into the tumour and no dispersion (Fig. 1B). Given the poor tolerance, inadequate penetration, and limited response measured by minimal aspiration of dissolved tumour, further treatments were abandoned, and the patient was discharged from hospital. The patient remains in a stable condition 3 months post-treatment.

Case 2

A 41-year-old male diagnosed with PMP in 2010 was treated surgically over the course of 6 years, which included peritonectomy with intraoperative chemotherapy and later pleurectomy with intraoperative chemotherapy for extra-abdominal recurrence. The latter was complicated by intrathoracic sepsis requiring a muscle flap. He presented with progressively worsening dyspnoea and chest pain. Recurrent disease was evident with multiple loculated pleural collections on CT imaging (Fig. 2A, C). Two 12-Fr pigtail drains were successfully

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inserted under radiological guidance into the right anterior chest tumours. BromAc® 30 mg/1.5 g formulated in 5% glucose, was equally distributed between the two drains with no reported severe adverse effects. A total of 5 doses of BromAc® were administered over a 2-week period. Local discomfort requiring oral analgesia was experienced. Approximately 890 mL of gelatinous material was aspirated per treatment. Following the completion of treatment at 2 weeks, the patient reported improvement in breathing, pain, and mobility. Objectively, this was visualised by significant reduction in tumour size on progress imaging (Fig. 2B, D). The patient is alive 6 months post-treatment. The patient is no longer under the direct care of our unit due to COVID-related travel restrictions.

Discussion

CRS combined with IPC offers potentially curative goals for peritoneal mucinous disease [1, 13]. Ideally, hyperthermic intraoperative thoracoabdominal chemotherapy (HITAC) is utilised if the diaphragm is compromised during cytoreduction; however, recurrence of disease with pleural involvement remains a possibility [2, 14, 15]. Surgical management should be considered for intrathoracic PMP; however, it may not be suitable for all patients. As such, the development of non-surgical management options for intrathoracic PMP is an important frontier.

The symptom burden of PMP largely stems from increasing mucin production that fills the locoregional space [4]. The ability to repeatedly drain that mucin would reduce symptoms in a disease that would inevitably be fatal due to complications arising from compression or erosion of vital organs and structures. Unlike ascites or pleural effusions which drain or aspirate easily, the high viscosity of mucin in PMP disease makes this very difficult. Sharma et al. [4] described a case demonstrating such difficulty despite the use of a 32-Fr intercostal chest tube.

Case 2 demonstrates the utility of BromAc® in dissolving and enabling drainage of mucin through only a 10- to 12-Fr drain. Objectively, this is noted in progress imaging demonstrating significant reduction in the loculated masses of the right thorax (Fig. 2). As detailed in the case history, the prior complex surgical history and anatomy had precluded further surgical management. The non-surgical approach utilised with BromAc® is likely to have offered the patient improved and extended quality of life given the limited options available. No direct serious adverse effects were observed during the use of BromAc®, further supporting the acceptable safety profile demonstrated in the Phase I trial investigating BromAc® use in peritoneal mucinous disease [8].

In contrast, the poor response in case 1 was likely due to the inherent hardness of the tumour with poor dissemination of drug. BromAc® has previously been documented to have improved efficacy in soft to intermediate textured tumours [8]. Mucin is a polymerous glycoprotein that can form many different crosslinks which provides these tumours with the ability to form highly complex structures with varying degrees of solidification. Unique crosslinks can be formed between the glycoprotein, salts and minerals, and various cell debris macromolecules. This creates heterogeneous tumours and mucin masses with theoretically varying degrees of response to mucolytic agents [11].

Conclusion

BromAc® represents an exciting treatment modality for patients with intrathoracic PMP who are not surgical candidates. Our preliminary data suggests that tumour hardness and texture may be significant factors in predicting treatment response, with greater drug dissem-

ination in soft to intermediate textured tumours. Further research into the link between treatment response and tumour characteristics will help guide future patient selection for BromAc® therapy.

Statement of Ethics

This study was conducted in accordance with local and national ethics protocols and regulations. Written consent was obtained from the patients for publication of this case report and all accompanying images. The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

Professor David L. Morris is the co-inventor and assignee of the Licence for this study and director of the spin-off sponsor company, Mucpharm Pty Ltd. Miss Sarah J. Valle is partly employed by Mucpharm for its cancer development and is supported by an Australian Government Research Training Program Scholarship.

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Author Contributions

Each author provided substantial contribution to the conception and design of the project, the acquisition and interpretation of data, and the drafting, and revision of the case report. Each author had final approval of the published version.

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