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**Case Report**

# Long-Term Treatment of Unresectable Pseudomyxoma Peritonei with Multiple Treatments of Intratumoural Bromelain and Acetylcysteine (BromAc®): A Case Report

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**Keywords**
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**Abstract**
Pseudomyxoma peritonei is a rare peritoneal malignancy characterized by the progressive accumulation of mucinous material and tumour within the abdomen and pelvis. Percutaneous drainage of mucin may be a non-surgical option for relief of symptoms; however, it remains difficult due to the high viscosity of mucin, with numerous case reports reporting difficulty removing material through medium-bore catheters alone. BromAc is a therapy currently undergoing development which dissolves mucinous tumour masses and allows for extraction. This report describes the case of a patient who has had multiple treatments with BromAc over 4 years.



## Introduction

Pseudomyxoma peritonei (PMP) is a rare peritoneal malignancy characterized by the progressive accumulation of mucinous fluid and tumour within the abdomen and pelvis. It is classically caused by rupture of appendiceal mucinous tumours but can also be associated with mucinous tumours of the ovaries and gastrointestinal tract [1].

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There is an unmet need for options in treatment of unresectable PMP. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy offer potentially curative goals for peritoneal mucinous disease. It may not be suitable however in all patients and increases in difficulty and complication rates with repeat operations [2]. Systemic chemotherapy is an alternative for unresectable disease but has limited efficacy due to PMP's borderline malignant potential, with studies suggesting an overall response rate of about 20%, a disease control rate of about 50–80%, and a median progression-free survival of about 7–8 months [3].

Percutaneous drainage of mucin may be a non-surgical option for relief of symptoms which are largely due to increasing mucin production and mass effect on surrounding organs [4]. It remains difficult however due to the high viscosity of mucin, with numerous case reports reporting difficulty removing material through medium-bore catheters alone [5, 6]. BromAc is a therapy currently undergoing development which dissolves mucinous tumour masses and allows for extraction. Bromelain is a combination of enzymes derived from the pineapple stem, known to cleave peptide and glycosidic bonds in mucin, while acetylcysteine reduces disulphide linkages in mucin [7]. It has recently undergone a clinical trial which demonstrated its safety and early outcomes with over 20 patients treated successfully [8]. This report describes the case of a patient who has had multiple treatments with BromAc over 4 years. The CARE Checklist has been completed by the authors for this case report, attached as an online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534202) [9].

## Case Report

A 66-year-old presented with nausea, vomiting, and decreased colostomy output on a background of recurrent appendiceal PMP with progressive disease and multiple abdominal and pulmonary lesions. In terms of his prior treatment, he had had two prior cytoreductive surgeries and hyperthermic intraperitoneal chemotherapy procedures in 2016 and 2017 with a peritoneal cancer index (PCI) score of 39 evident in both and the second procedure complicated by intraperitoneal sepsis and abdominal-wall mesh infection. He also underwent treatment with two doses of BromAc in 2019 when he was considered unsuitable for further surgical management. At this time, the drain was dislodged following two injections of BromAc; however, there was a small response when measured by volume of tumour aspirated (total of 15 mL), and a small reduction in tumour size was visible on computed tomography scan. Throughout the next 2 years, the patient was asymptomatic.

A computed tomography scan was performed, demonstrating evidence of a high-grade bowel obstruction and multiple collections in the pelvis. A drain was inserted into the largest collection (14-Fr pigtail drain) under radiological guidance. A total of 5 doses of BromAc was administered over 5 days, with the volume administered differing each time as shown in Table 1. The patient was premedicated with an oral antihistamine (loratidine 10 mg) and paracetamol 1 g 1 h prior to BromAc administration. Bromelain 90 mg and acetylcysteine 2 g were reconstituted and administered in 5% dextrose through a sterile Millex 0.22-μm syringe filter to remove debris. The drug was allowed to dwell for 24 h before being drained, and repeat treatment considered. The volume injected, as tolerated, was aimed at 20% of the target tumour volume. Approximately 50–150 mL of clear/white gelatinous material with some blood staining was aspirated per treatment. The volumes of mucinous material aspirated are also listed in Table 1.

He experienced 1 episode of fever to 38.9°C on day 2 of treatment. At this time, blood tests revealed an elevated white count of $19.7 \times 10^9$/L, an elevated CRP of 266 mg/L, and decreased

**Table 1.** Volumes of BromAc administered and mucinous material aspirated

| Treatment | Bromelain administered | Acetylcysteine | Volume aspirated (24 h later) |
|---|---|---|---|
| 1 | 20 mg | 0.4 g | 60 mL |
| 2 | 70 mg | 1.6 g | 150 mL |
| 3 | 50 mg | 1.1 g | 120 mL |
| 4 | 50 mg | 1.1 g | 120 mL |
| 5 | 45 mg | 1 g | 115 mL |
| 6 | – | | 50 mL |

albumin at 28 g/L. He was commenced on empirical antibiotics. A septic screen was negative, and the fever resolved with paracetamol following a few hours.

A significant reduction in tumour size was visualized on progress imaging (Fig. 1). His obstructive symptoms also resolved during treatment with BromAc. He was nil by mouth with supportive intravenous fluids for a total of 3 days, following which his diet was gradually upgraded and intravenous fluids weaned. He was tolerating a full diet with improved stoma output 2 days following drain insertion.

In total, he was admitted for 13 days. He was discharged 2 days following the final administration of BromAc and was then followed up in clinic 1 month post-discharge. His bowel obstruction did not recur; however, he did experience progression of his pelvic collections and underwent two further BromAc treatments 1 year following this episode. These treatments are not described in detail in this report; however, they were both similarly uncomplicated and effective in reducing tumour volume.

## Discussion

This case demonstrates the efficacy and safety of multiple treatments with intra-tumoural BromAc over an extended period in unresectable PMP, an area in which there is currently limited literature, given the rarity of the condition and the novelty of the drug which has only recently undergone a phase 1 trial. While report of this trial included patients with repeat treatments within a year [8], this study details a patient who has received a total of four treatment courses of BromAc with follow-up over 4 years which has not been reported on previously.

The efficacy is seen in both resolution of symptoms and objective findings including a reduction in tumour size on progress imaging and volume of mucin aspirated, which totalled 615 mL. While another case series has demonstrated successful drainage of PMP in 4 patients with interventional radiology techniques [5], these were with the use of large or multiple catheters and aggressive suction which were not required in this case.

The safety of BromAc is additionally supported by this case, with the only adverse effect being a fever which self-resolved and no adverse events in further BromAc treatments the year following this episode. Fever was also seen in 35% of patients in the phase 1 trial [8] and is possibly due to the dissolution of tumour or inflammation at treatment sites. This inflammatory reaction has also been reflected in other patients with decreased albumin and increased white cell count and CRP [10].

The strengths of this study are its applicability to clinical practice and evidence supporting a novel treatment for a life-threatening condition in which it is difficult to perform randomized controlled trials due to its rarity. The main limitations however are that the level

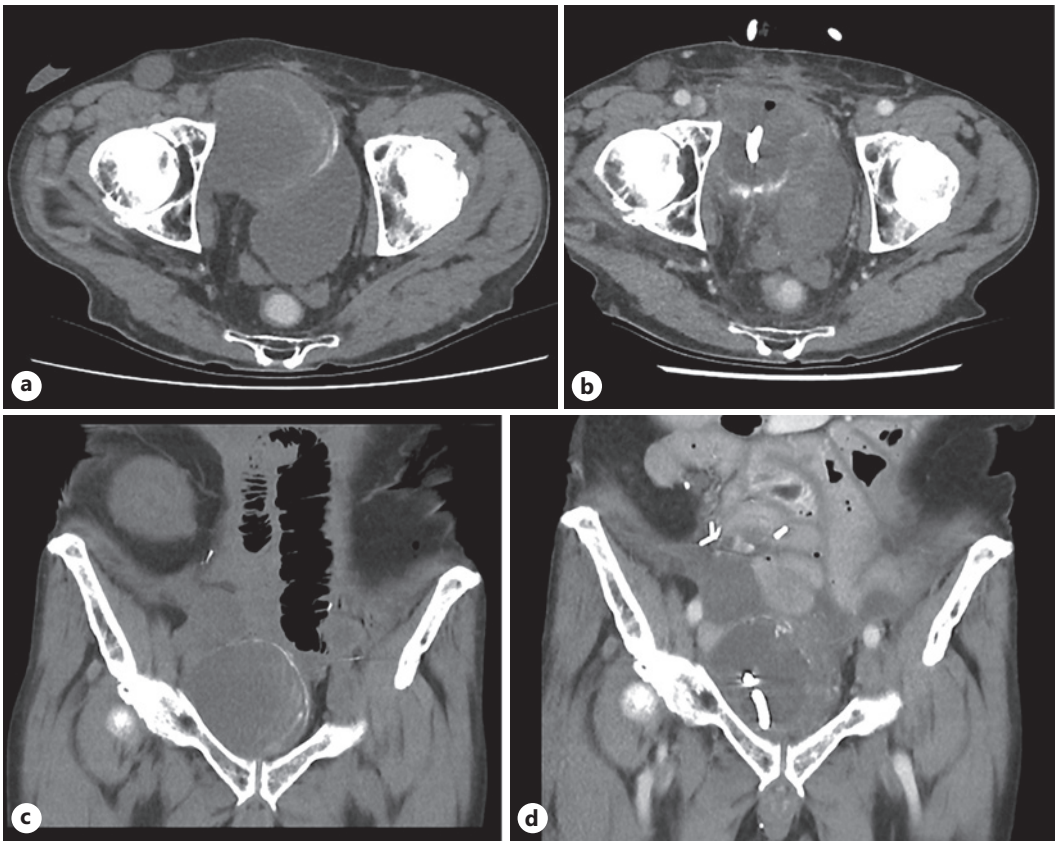


**Fig. 1.** CT pre- and post-treatment. Progress scan on right (**b**, **d**). Multiple mild peripherally enhancing collections demonstrated within the pelvic, largest of which in the left posterior pelvic measures 80 × 39 mm trans-axially (previously 85 × 55 mm). The anterior pelvic collection has reduced in size with a pigtail tube in situ, now measuring 57 × 51 mm trans-axially (previously 71 × 69 mm). Scan 1: October 21, 2021, scan 2: October 13, 2021. CT, computed tomography.

of evidence is low and reproducibility is uncertain as a single retrospective case report. This patient had disease amenable to long-term treatment with BromAc and aspiration of mucin with minimal adverse effects; however, this is difficult to generalize without a larger sample size. Caution must also be made regarding over-interpretation of results as a direct cause and effect relationship between treatment with BromAc, aspiration of mucin, and radiological and symptomatic improvement cannot be inferred with certainty. This patient's bowel obstruction may have resolved without BromAc, and there is no control sample to compare to.

The patients in whom this treatment would be most advantageous for and most effective and safe in are also still not clear. Patients with recurrent or unresectable PMP often have complicated disease with varying anatomical characteristics such as location, loculation, and erosion into surrounding structures [8] and varying physical and chemical characteristics of mucin [11] which can all make administration of BromAc and dissolution and aspiration of tumour more difficult. These can lend themselves to serious adverse events as seen in the initial case series, such as fistula creation with dissolution of tumours that have eroded into the gastrointestinal or genitourinary tract. These are detailed further in previous reports [8, 12], however emphasizing the importance of patient selection, completion of procedures with experienced interventional radiologists and clinicians, and close monitoring post-treatment for expedient identification and treatment of adverse events. Further research into how to

identify these risks prior to drain insertion and administration of BromAc will aid in improving the performance of this treatment and establishing it as an alternative treatment for inoperable PMP.

## Conclusion

Intra-tumoural administration of BromAc is a new and minimally invasive treatment for inoperable mucinous tumours. This case demonstrates the safe and effective treatment of a patient with multiple treatments of BromAc over 4 years. Further research on the outcomes and efficacy of treatment, both short-term and long-term, would aid in establishing BromAc as an alternative treatment for inoperable PMP.

## Statement of Ethics

This study was conducted in accordance with local and national ethics protocols and regulations. The patient received treatment as part of a phase 1 trial which received ethics approval by Bellberry Ltd. and is registered at ClinicalTrials.gov (NCT03976973) and anzctr.org.au (ACTRN12617001612303). Written informed consent was obtained from the patient for publication of the case report and all imaging studies.

## Conflict of Interest Statement

Professor D.L. Morris is the co-inventor and assignee of the intellectual property and co-owner and director of the company Mucpharm Pty Ltd. which produces BromAc and sponsored the original clinical trial. Ms S.J. Valle is co-owner of Mucpharm Pty Ltd.

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## Author Contributions

Jessica Yang, Sarah Valle, Derek Glenn, Suhrid Lodh, and David Lawson Morris were all involved in conceptualisation, interpretation, writing, and editing of the work. Suhrid Lodh, Derek Glenn, and David Lawson Morris contributed significantly to patient treatment and acquisition of data for the work.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

## References

1 Bartoška P, Antoš F, Vítek P, Marx J, Kopic J, Holečková P. Pseudomyxoma peritonei. Klin Onkol. 2019;32(5):329–32.
2 Govaerts K, Lurvink RJ, De Hingh I, Van der Speeten K, Villeneuve L, Kusamura S, et al. Appendiceal tumours and pseudomyxoma peritonei: literature review with PSOGI/EURACAN clinical practice guidelines for diagnosis and treatment. Eur J Surg Oncol. 2021;47(1):11–35.
3 Hiraide S, Komine K, Sato Y, Ouchi K, Imai H, Saijo K, et al. Efficacy of modified FOLFOX6 chemotherapy for patients with unresectable pseudomyxoma peritonei. Int J Clin Oncol. 2020;25(4):774–81.
4 Rizvi SA, Syed W, Shergill R. Approach to pseudomyxoma peritonei. World J Gastrointest Surg. 2018;10(5):49–56.
5 vanSonnenberg E, Goodacre BW, Wittich GR, Ali S, Silverman SG, Shankar S, et al. Interventional radiology strategies in the treatment of pseudomyxoma peritonei. Cardiovasc Intervent Radiol. 2005 2005/05/01;28(4):490–4.
6 Sharma DK, Ram D, Shukla H, Rajappa SK, Darlong LM. Pseudomyxoma pleuri as a surgical emergency: a rare case report. Indian J Surg Oncol. 2018 2018/06/01;9(2):271–3.
7 Pillai K, Akhter J, Morris DL. Assessment of a novel mucolytic solution for dissolving mucus in pseudomyxoma peritonei: an ex vivo and in vitro study. Pleura Peritoneum. 2017;2(2):111–7.
8 Valle SJ, Akhter J, Mekkawy AH, Lodh S, Pillai K, Badar S, et al. A novel treatment of bromelain and acetylcysteine (BromAc) in patients with peritoneal mucinous tumours: A phase I first in man study. Eur J Surg Oncol. 2021;47(1):115–22.
9 Riley DS, Barber MS, Kienle GS, Aronson JK, von Schoen-Angerer T, Tugwell P, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017;89:218–35.
10 Ke K, Pillai K, Mekkawy A, Akhter J, Badar S, Valle S, et al. The effect of intraperitoneal administration of BromAc on blood parameters: phase 1 study. Discov Oncol. 2021;12(1):25.
11 Pillai K, Akhter J, Mekkawy A, Chua TC, Morris DL. Physical and chemical characteristics of mucin secreted by pseudomyxoma peritonei (PMP). Int J Med Sci. 2017;14(1):18–28.
12 Wen HK, Valle SJ, Morris DL. Bromelain and acetylcysteine (BromAc(®)): a novel approach to the treatment of mucinous tumours. Am J Cancer Res. 2023;13(4):1522–32.