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Case Report

# Novel Use of Intravesical Bromelain and N-acetylcysteine for Pseudomyxoma Peritonei with Bladder Involvement: Case Series

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## Abstract

**Introduction:** Pseudomyxoma peritonei (PMP) is a rare and challenging neoplastic condition associated with great morbidity when left untreated. The standard treatment is cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC). However, not all patients are suitable candidates for extensive operative management, necessitating alternative avenues to symptom management. Bromac is a combination of bromelain and N-acetylcysteine which demonstrates mucolytic effects and has been shown to alleviate the compressive effects of PMP.

**Case Presentation**: This case series describes the symptomatology and history of two patients with PMP with bladder involvement. Due to a combination of personal and medical factors, these patients sought alternatives to operative management. We detail the novel treatment of PMP with intravesical Bromac and the clinical response to this therapy.

**Conclusion**: This case series demonstrates a symptomatic and radiological improvement when intravesical Bromac is used to manage PMP with bladder involvement. Further research is required to polish the dosing, frequency, and method of administration

**Keywords**: Bromelain; Acetylcysteine; Pseudomyxoma Peritonei; Bladder; Peritonectomy

## Introduction

Pseudomyxoma peritonei is a neoplastic phenomenon with an estimated incidence of 1-3 in 1,000,000 per year [1]. It is characterized by excessive mucinous ascites that, if left untreated, result in mass compression, organ dysfunction, and malnutrition. Appendiceal cancer is the most common culprit, although this clinical syndrome may also be elicited by ovarian, pancreatic, or colorectal tumors [2].

As it stands, cytoreductive surgery and HIPEC offer the most favorable survival outcomes, although this is only appreciable in select populations due to high postoperative morbidity. Operative suitability is determined by a combination of patient and tumor factors such as baseline function, comorbidities, the extent of metastasis, and disease resectability [3]. There is therefore an impetus to investigate other avenues for management.

Unfortunately, PMP exhibits a poor response to systemic chemotherapy. This is likely attributable to the carcinogenic and chemoresistant properties of the mucinous barrier lining neoplastic cells [4]. This has prompted researchers to explore the role of mucolytic therapies in optimizing chemosensitivity, as well as disintegrating high-volume mucinous disease in non-operative candidates [5].

Mucin 2 (MUC2) is a significant constituent of PMP mucin

(amongst MUC1 and MUC5AC) which has become an appealing target for mucolytic therapy. It is a glycoprotein composed of peptide, disulfide, and glycosidic bonds. Bromac, a combination of bromelain and N-acetylcysteine, has shown promise in the treatment of PMP. Bromelain is a cocktail of proteolytic and non-proteolytic enzymes extracted from the stems of pineapple plants, that hydrolyses glycosidic bonds, amides, and esters. N-acetylcysteine is an amino acid naturally found in Allium plant species which reduces disulfide bonds between MUC2 bonds. Together, they compromise the structural integrity of mucin [4,6,7]. The mucolytic effects of bromac have been demonstrated in both ex-vivo and in-vivo studies [8]. The safety of Bromac has also been demonstrated in Phase 1 trials, with the most common adverse effects including a rise inflammatory markers, febrile reaction, and pain. Serious adverse effects occurred in 12.5% of patients. These included but were not limited to, hypoalbuminemia (requiring albumin infusions), sepsis, and gastrointestinal fistulas. No treatment-related deaths were reported. [9].

Bromac has seen use in rare cases of intrathoracic PMP [10], but has never before been used in bladder involvement. This case series discusses the novel use of intravesical Bromac for the management of urinary symptoms in patients with PMP bladder invasion.

## Case 1

A 41-year-old male with a background of recurrent appendiceal cancer and PMP presented to the emergency department with two weeks of increasing urinary frequency, difficulty voiding, and mucinous discharge from his urethra and rectal stump. He also reported intermittent symptoms of bowel obstruction including reduced stoma output, abdominal pain, and nausea. On examination, he was noted to have a large abdominal wall mass measuring approximately 10cm in diameter in the left mid-abdomen. A computer tomography (CT) of his abdomen and pelvis revealed lobulated lesions at the rectovesical pouch, and larger lobulated masses posterior to the rectus abdomini muscles measuring 56x118mm indicative of progressive mucinous disease (Figure 1).

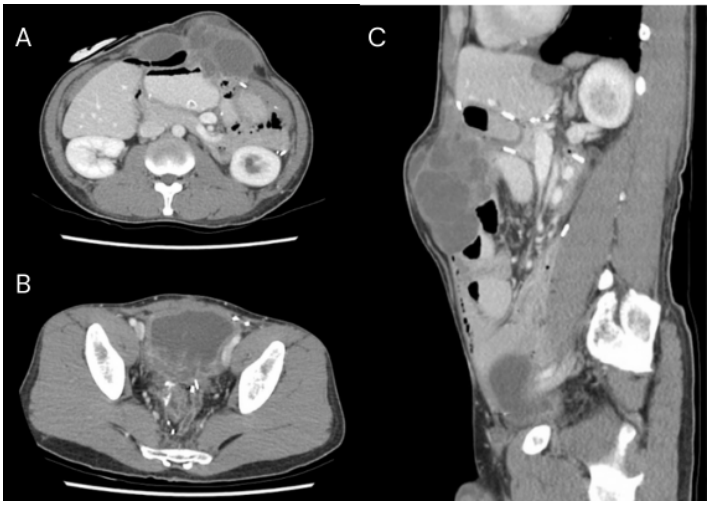


**Figure 1:** Delayed portal venous CT view showing A) invasion of PMP into rectus abdominal muscles (axial view), B) Bladder and rectal stump involvement of PMP (axial view), C) PMP involvement of anterior abdominal wall (sagittal view)

This patient had a history of two previous peritonectomies in 2013 and 2015. He was planned for a re-do peritonectomy in 2021, however when informed he may have required a urostomy due to invasion of his bladder dome, he declined operative management and discharged against medical advice.

Given this patient's aversion to receiving a urostomy, he consented to treatment with intravesical Bromac. Prior to this, a retrograde cystogram was performed, which excluded a rectovesical fistula (Figure 2).

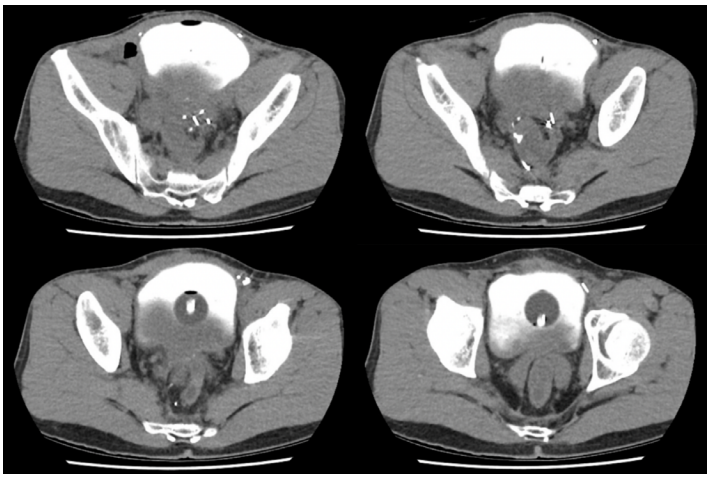

**Figure 2:** Four axial slices of post-contrast CT cystogram demonstrating filling defect in posterior aspect of the bladder due to mucinous disease. No contrast extravasation to rectal stump noted.

The Bromac solution was prepared by mixing 100mg of bromelain with 10 ml of sodium chloride 0.9%. This was injected in 500ml of glucose 5% using a minisart syringe filter. 10ml of N-acetyl cystine was then mixed with the glucose/bromelain preparation. This was administered via a three-way catheter, which was then spigotted.

Due to symptoms of bladder fullness and urinary urgency, the patient was unable to tolerate large boluses of the Bromac solution. As such, a decision was made to administer small volumes of Bromac twice daily over three days. Given the novel use of Bromac, there were no protocolized guidelines regarding volume and length of treatment. In this case, the volume administered and duration of therapy (i.e. how long the catheter remained spigotted) were determined by patient symptoms (Table 1). Following administration of Bromac, the patient reported referred discomfort and fullness at the site of his mucinous abdominal wall invasion. He also reported dizziness and a generalized feeling of warmth – both of which were transient and self-limiting.

| Day of administration | Dose number | Volume (ml) | Duration of therapy (minutes) |
|---|---|---|---|
| Day 1 | 1 | 110 | 160 |
| Day 1 | 2 | 120 | 160 |
| Day 2 | 3 | 130 | 177 |
| Day 2 | 4 | 120 | 125 |
| Day 3 | 5 | 80 | 150 |
| Day 3 | 6 | 70 | Not recorded |

**Table 1:** Case 1 - Volume and duration of Bromac administration.

Following the three days of intra-vesical Bromac therapy, a repeat cystogram was performed (Figure 3) which showed a small decrease in mucin and no evidence of bladder wall dissolution. 7 days following his last dose of bromac, the patient reported a subjective improvement in his urinary symptoms.

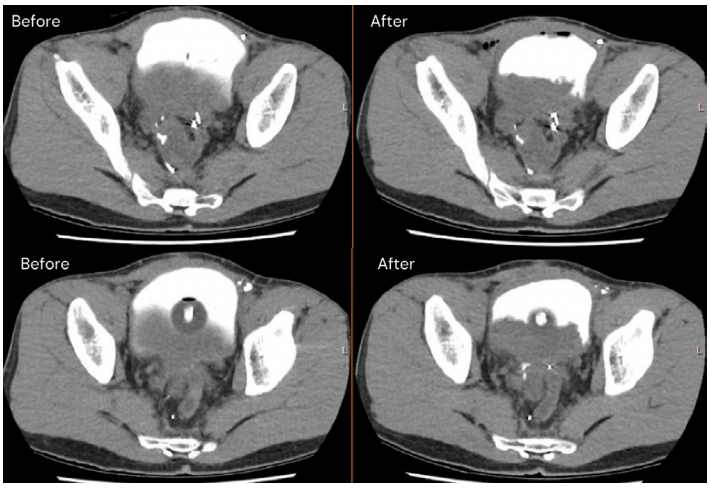


**Figure 3:** Left-pre-Bromac scan, Right-post-Bromac scan.

## Case 2

Our second case details the use of intra-vesical Bromac in a patient who had undergone six previous peritonectomies, most recently in 2013, for recurrent appendiceal cancer and PMP. The mucinous invasion into his bladder resulted in chronic obstructive uropathy, leading to symptoms of mucinuria, urinary urgency, hesitancy, and incomplete voiding. Furthermore, he had developed a rectovesical fistula resulting in mucinous discharge from his rectal stump. His severe ureteric structuring and recurrent mucinous blockages necessitated multiple rounds of ureterolysis and six-monthly stent exchanges. A re-do peritonectomy would have necessitated ureteric reconstruction and an ileal conduit formation. However, given the impaired quality of his ureters, he was deemed ineligible for operative management. The patient therefore agreed to a trial of intra-vesical Bromac.

A baseline CT cystogram was performed (Figure 4). The Bromac solution was prepared with the same dosage and mechanism as described in Case 1. Similarly, this was administered twice daily, and the volumes and duration of therapy was guided by patient comfort (Table 2). The patient received three days of Bromac and underwent a progress CT cystogram (Figure 4), then completed a fourth day of Bromac therapy given his symptomatic improvement just after 3 days with minimal adverse effects.

| Day of administration | Dose number | Volume (ml) | Duration of therapy (minutes) |
|---|---|---|---|
| Day 1 | 1 | 120 | 175 |
| Day 1 | 2 | 90 | 125 |
| Day 2 | 3 | 120 | 120 |
| Day 2 | 4 | 120 | 120 |
| Day 3 | 5 | 120 | 125 |
| Day 3 | 6 | 120 | 120 |
| Day 4 | 7 | 120 | 120 |
| Day 4 | 8 | 120 | 120 |

**Table 2:** Case 2 – Volume and duration of Bromac treatment.

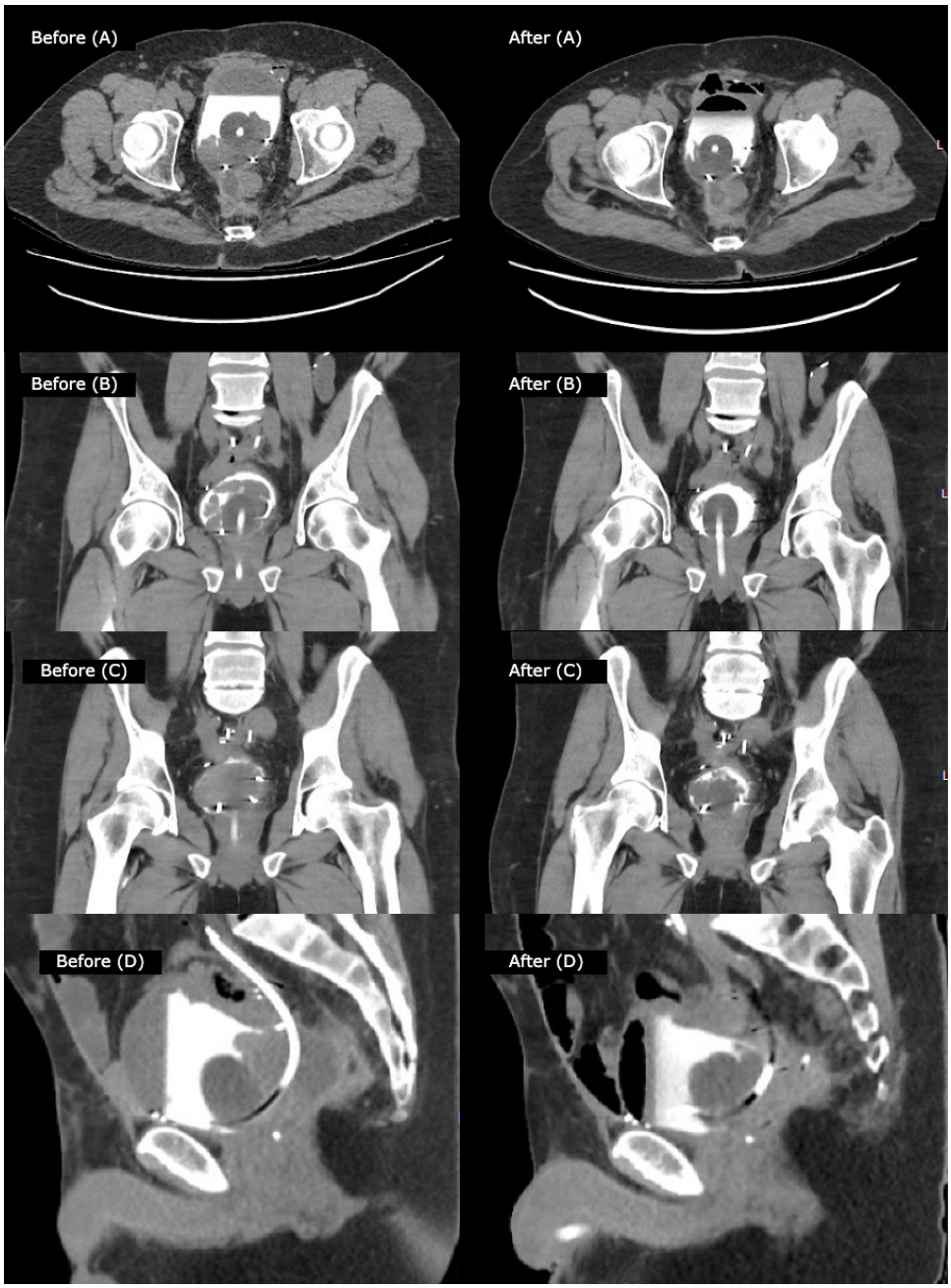


**Figure 4:** CT cystogram slices comparing mucinous disease before and after Bromac therapy. Axial (A), coronal (B, C), and sagittal (D) views.

The patient reported symptoms of 'bladder spasms' during and after Bromac administration. Given he reported similar symptoms when receiving contrast for his baseline cystogram, this was thought to be a distension-related symptom rather than a direct adverse effect of the Bromac itself. No other adverse effects were reported.

The International Prostate Symptom Score (IPSS) was used as a proxy to quantitate the symptomatic difference before and one week after Bromac treatment. On his baseline questionnaire, the patient scored 17 and 3 on the symptom severity and quality-of-life scale respectively. The post-bromac questionnaire improved the overall severity of symptoms to a 4 and quality of life to a 1 (supplementary material).

## Discussion

These cases describe an unprecedented approach to managing urinary symptoms in patients with PMP invading the bladder wall. After three days of intravesical Bromac, both patients reported a subjective improvement in urinary frequency and less difficulty voiding. Case 2 showcases a notable radiological improvement following Bromac therapy. This demonstrates a role for intravesical Bromac in non-surgical candidates, although further studies are warranted to refine treatment protocol, including the dosage, volume, and duration of treatment. Long-term data would also be valuable in determining the interval between repeat cycles of Bromac therapy.

In these cases, treatment efficacy may have been limited by the duration that Bromac was given to take effect, as well as its dilution by urine. Continuous bladder irrigation (CBI) may increase the contact time of Bromac with the bladder wall and provide more consistent drug concentrations. This may require greater volumes of Bromac, which may incur greater costs. Alternatively, the use of percutaneous nephrostomies would offer a more concentrated intravesical administration of Bromac by diverting urine flow from the renal pelvis. Lower volumes of Bromac would be required to achieve the same concentrations as CBI, at the expense of a more invasive technique. These options would be useful in standardizing treatment dose and duration, and guiding future applications.

One critical consideration in the use of intravesical Bromac is the risk of bladder wall dissolution. While the presented cases exhibited a subjective improvement in symptoms, the long-term ramifications of mucinous breakdown on bladder integrity, bladder function, and overall quality of life, remain tentative. Future studies should focus on optimizing treatment protocols to achieve the desired therapeutic effects while minimizing the risk of further bladder injury, and other possible complications. Undoubtedly, such protocols would have to be calculated based on the extent of mucinous invasion.

## Conclusion

Intravesical administration of Bromac represents a novel and potentially promising approach for managing urinary symptoms in patients with PMP invading the bladder wall. While these case series offer insight into its feasibility and safety, further research and clinical trials are needed to polish the protocol and determine its efficacy, and possible adverse effects.

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**Ethics**: This study was conducted under the Compassionate Use Program of the Therapeutic Goods Administration special access scheme (approval number 201707561). Written informed consent was obtained from both patients for publication of the details of their medical care and any accompanying images.

**Conflict of Interest**: David Morris is the co-founder of Mucpharm Pty Ltd. Sarah Valle is an employee of Mucpharm.

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