Asian Journal of Epidemiology

ISSN 1992-1462

science alert
http://www.scialert.net

ANSInet
an open access publisher
http://ansinet.com

OPEN ACCESS Asian Journal of Epidemiology

ISSN 1992-1462
DOI: 10.3923/aje.2024.1.5

Case Study
Application of Recombinant Human Activated Protein C in Severe Pseudomembranous Colitis-Case Report

Dariusz Onichimowski, Paweł Radkowski, Marcin Mieszko Mieszkowski and Damian Bronisław Truszczyński

Department of Anesthesiology and Intensive Care, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland

Abstract

Clostridium difficile is a common pathogen known to cause colitis and antibiotic-associated diarrhea. Its toxins can lead to pseudomembranous colitis, characterized by persistent, occasionally bloody diarrhea, fever, leukocytosis and hypoalbuminemia. Severe cases may progress to sepsis, necessitating hospitalization and ICU care. This case report aims to describe the management of pseudomembranous colitis, focusing on a patient with severe sepsis, where conventional antibiotic discontinuation is challenging due to the need for appropriate antibiotic therapy. A case of pseudomembranous colitis was presented with severe sepsis in a patient who required continued antibiotic therapy. The patient's clinical course, diagnostic findings and treatment strategy, including the use of Recombinant Human-Activated Protein C (rhAPC), are detailed. In patients with pseudomembranous colitis complicated by severe sepsis, the decision to discontinue antibiotics must be carefully weighed against the need for effective treatment. The addition of rhAPC to appropriately targeted antibiotic therapy, as recommended by the Surviving Sepsis Campaign in cases of septic shock with organ failure, may offer a valuable therapeutic option due to its anti-inflammatory, antithrombotic and profibrinolytic properties. Further research is needed to determine the optimal management approach in such challenging cases.

Key words: Pseudomembranous colitis, sepsis, systemic inflammatory response syndrome, recombinant human activated protein C, *Clostridium difficile*

Citation: Onichimowski, D., P. Radkowski, M.M. Mieszkowski and D.B. Truszczyński, 2024. Application of recombinant human activated protein C in severe pseudomembranous colitis-case report. Asian J. Epidemiol., 17: 1-5.

Corresponding Author: Damian Bronisław Truszczyński, Department of Anesthesiology and Intensive Care, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Clostridium difficile is a common pathogen and etiological factor of colitis and antibiotic-associated diarrhoea, as it is widespread in the environment (soil, water, hospital environment, animal and human gastrointestinal tract). *Clostridium* toxins can cause pseudomembranous colitis with persistent, occasionally bloody, diarrhoea, accompanied by fever, leukocytosis and hypoalbuminemia. Rarely *C. difficile* infection (CDI) may result in complications such as haemorrhage, toxic megacolon and bowel perforation. Severe sepsis may sometimes develop in the course of the disease, which requires hospital admission and management in the ICU. In the recent years, CDI incidence has increased both in ICU and general patient population. Severity of infection also increased, as well as the number of patients admitted to the ICUs due to complications associated with CDI[1]. Based on data from the National Inpatient Sample, there was a twofold increase in the diagnosis of CDI in U.S. hospitals from 2000 to 2005, reaching a rate of 11.2 cases per 10,000 population. Similarly, the age-adjusted CDI mortality exhibited a parallel trend, rising from 1.2% in 2000 to 2.2% in 2004[2]. In the ICU setting, overall, 30-day mortality in patients with CDI reached almost 40% in 2004 and 2005. In case control studies it was estimated that in critically ill patients 6% mortality was directly attributable to CDI[3].

Patients suffering from pseudomembranous colitis require aggressive management in the ICU setting not only due to CDI but also as a result of infection that confounds the primary disease. Apart from oral anti-*Clostridium difficile* agents, the cornerstone of medical management of pseudomembranous colitis is the discontinuation of an offending antibiotic. In patients with severe sepsis, prompt initiation of appropriate antibiotic therapy is crucial, thus full discontinuation of antibiotics is impossible. In septic shock presenting with failure of at least two organs the Surviving Sepsis Campaign recommended Recombinant Human Activated Protein C (rhAPC) added to appropriately targeted antibiotic therapy.

The rhAPC is a serine protease with anti-inflammatory, antithrombotic and profibrinolytic properties. It modulates inflammation and thrombosis at the level of microcirculation, largely limiting inflammation-induced tissue damage. It also facilitates tissue repair. To our knowledge, no reports regarding rhAPC administration in pseudomembranous colitis have been published in medical literature as yet.

Case of 55-year-old female with severe colitis triggered by *C. difficile* is presented, who required hospitalization in the ICU as a result of an accompanying severe chest infection complicated by septic shock. In addition to standard medication, rhAPC was administered and the patient's general condition improved significantly, chest infection was cured and large bowel inflammation healed, despite continued antibiotic treatment.

CASE PRESENTATION

A 55-year-old female patient was admitted to the ICU because she presented severe respiratory distress symptoms caused by severe bilateral pneumonia with bilateral pleural effusion as a consequence of pseudomembranous colitis. The first symptoms of CDI appeared two weeks before the admission to the ICU. Initially, the patient was admitted to the infectious diseases department of a district hospital as she manifests abdominal pain, vomiting, diarrhoea and high fever. Two months earlier the patient had been treated with antibiotics (clindamycin) because of stomatitis. After three days spent in the infectious diseases department, the patient was transferred to the surgical department due to lack of improvement. Laparotomy was performed and revealed the inflamed bowel. *Clostridium difficile* toxins A and B were identified in the faeces. Active inflammatory lesions forming numerous, separated, slightly raised, white-yellowish 2-9 mm plaques were found on colonoscopy in the entire large intestine. The surrounding mucosa was dry, swollen and red. On day 15 the patient was transferred to the ICU of the Regional Specialist Hospital in Olsztyn, because she developed severe chest infection as a complication of pseudomembranous colitis.

On admission, she was unwell but conscious, with severe dyspnoea at rest, which impeded speaking. On passive oxygen therapy, arterial blood gases showed hypocapnia and hypoxemia. Physical and radiological features of severe bilateral pneumonia with pleural effusion were found. The abdomen was distended but soft and non-tender on palpation. Bowel sounds were poorly audible. Pitting oedema of the back was noted. The patient was intubated and ventilated (SIMV- Synchronised Intermittent Mandatory Ventilation; FiO_2 0.6; PEEP-Positive End-expiratory Pressure 8 mbar). Intravenous metronidazole 0.5 g QID and vancomycin 0.5 g QID via NGT were continued. Substitution dose of IV hydrocortisone 50 mg QID was also given and total parenteral nutrition was instituted. Regarding severe chest infection and *Escherichia coli* positive blood culture, intravenous piperacillin/tazobactam 4.5 g TID and azithromycin 0.5 g once daily were commenced. Moreover, a single dose of 100 mL 20% albumin was infused because of profound hypoalbuminemia (18.3 g/L). Physiotherapy and bronchoalveolar lavage (BAL) were performed several times. Tuberculosis was excluded.

Despite extensive treatment, no improvement was observed. Pulmonary lesions were still present with pleural effusion on repeat chest X-ray. On day 10 control colonoscopy limited to the left colon was performed. Persistent active inflammatory lesions consistent with pseudomembranous colitis were found. The patient's general condition gradually deteriorated, with continuously high WBC, CRP and PCT levels. Features of imminent multiple organ failure and septic shock were observed and confirmed by PiCCO (Pulse Contour Cardiac Output) monitoring. It was necessary to put her on IV dobutamine and norepinephrine to maintain adequate tissue perfusion. Ventilation (FiO_2 1.0; PEEP 12-15 mbar) had to be intensified because of increasing hypoxemia and IV furosemide was administered regarding emerging oliguria.

Diarrhoea persisted: As standard treatment was unsuccessful, rhAPC was introduced on ICU day 10, (drotrecogin alfa, Xigris, Eli Lilly, Switzerland) in a dose recommended by the Surviving Sepsis Campaign (24 µg/kg b.wt., per hour infusion for 96 hrs). The targeted antibiotic therapy was continued. Subsequently diarrhoea stopped, inflammatory parameters decreased and the patient improved. Catecholamines were discontinued and mechanical ventilation was reduced. During IV rhAPC treatment, neither GI bleeding nor other haemorrhagic complications were observed. As kidney failure features were still present and the patient suffered from hyperhydration (water intoxication), continuous renal replacement therapy was introduced (day 16 through 23). On ICU day 16, tube feeding was gradually introduced (Nutrison Peptisorb, Nutricia) along with supplemental partial parenteral nutrition. On day 26 repeat colonoscopy was normal.

Despite general improvement, the patient still required ventilation support (CPAP, SIMV). Complete cessation was impossible due to recurrent VAP with fluid collecting in the pleural cavity (confirmed on repeat chest X-ray and CT scan). On ICU day 24 percutaneous tracheostomy was performed. Mechanical ventilation was stopped on day 30 and parenteral nutrition was discontinued on day 36. A simple diet was started orally and was well tolerated. After removing the tracheotomy tube, the patient was transferred to the gastroenterology department. She was well, alert, with normal pulmonary and circulatory function, with neither diarrhoea, nor features of severe infection and peritonitis.

DISCUSSION

Clostridium difficile infection causes inflammation in the large intestine and diarrhoea as a result of GI luminal exotoxin secretion. Toxin A (TcdA) induces neutrophil migration, intestinal wall inflammation, necrosis and mucosal damage[2]. Toxin B (TcdB) exerts a similar destructive cytotoxic impact on the large bowel wall, yet it is approximately 10 times more potent[2]. Binding to membrane receptors on colonocytes, *C. difficile* exotoxins undergo endocytosis and induce cell actin cytoskeleton degradation via intracellular GTPase, which subsequently leads to cell death[1]. Apart from the intracellular effects of *C. difficile* binding to membrane receptors of the intestinal epithelium, the exposition of colonocytes to TcdA stimulates the migration of neutrophils, inflammatory infiltration and increased secretion of inflammatory mediators (e.g., chemokines, interleukin-8 and TNF-alpha)[2]. Exposition of colonocytes to TcdA induces increased release of substance P from submucosal primary sensory intestinal neurons and mast cell activation[1]. All above mentioned processes intensify inflammation which develops in the intestinal wall and can lead to SIRS (Systemic Inflammatory Response Syndrome)[1]. Both TcdA and TcdB are involved in disruption of colonocyte tight junctions that results in intestinal epithelium damage. Both toxins have ability to trigger apoptosis of intestinal wall cells[1]. Desquamated colonocytes, inflammatory cells and protein effusion form pseudomembranes visible on colonoscopy in CDI patients.

The patient developed respiratory insufficiency associated with pseudomembranous colitis. Lung dysfunction was most likely due to hypoalbuminemia with bilateral fluid retention in pleural cavity and chest infection as a result of atelectasis. Additional factor facilitating chest infection was *E. coli* bacteremia caused by mucosal barrier destruction and bacterial translocation, as well as Gram-negative bacteria selection due to earlier prolonged clindamycin administration. Consequently, the patient was admitted to the local ICU. Despite continued pseudomembranous colitis treatment with vancomycin and metronidazole she developed SIRS and subsequently septic shock symptoms. The SIRS could have resulted from both the large bowel inflammation and chest infection. The SIRS and septic shock were most likely the results of both factors acting simultaneously. However, the typical treatment mode of severe CDI according to the Society of Infectious Diseases Pharmacists recommendations[4] appeared to be ineffective, probably due to further antibiotic administration, as it could not be discontinued. The multi-organ inflammatory process further led to considerable worsening and triggered multiple organ failure (APACHE II score: 27) so rhAPC was introduced following the Surviving Sepsis Campaign guidelines. Multi-centre randomized placebo-controlled phase III trial showed that post-rhAPC 28 day mortality rate decreased in patients with severe sepsis and high mortality risk (APACHE II>25)[5]. In current case study,

rhAPC infusion resulted in general improvement and decreased inflammation that enabled catecholamine discontinuation and assisted ventilation reduction. Considerable regression of pulmonary lesions was revealed on X-ray imaging and total mucosal healing were shown on colonoscopy. Accordingly, diarrhoea responded to treatment.

The RhAPC demonstrates activity comparable with endogenic active protein C. Activated protein C (APC) is a serine protease with anticoagulant and anti-inflammatory properties. The APC and its cofactor, protein S, inactivate factors Va and VIIa, thus limiting thrombin production. Excessive activation of coagulation plays an important role in septic shock pathophysiology. Limiting this activation, APC considerably improves microcirculation in the inflamed tissue. The anti-inflammatory activity of APC is based on limited pro-inflammatory cytokine secretion such as TNF-alpha, IL-6 and IL-8. Moreover, APC inhibits leukocyte chemotaxis, adhesion and activation[6,7]. As an anti-inflammatory factor, APC counteracts TcdA activity. Additionally, APC inhibits the destruction of collagen due to the excessive production of collagenase stimulated by TNF-alpha[6]. Thus, APC can counteract the stimulation of inflammatory processes caused by *C. difficile* exotoxins. Improving microcirculation and inhibiting collagen degradation in the intestinal wall, APC is likely to accelerate healing. The APC inhibits apoptosis, directly influences the rebuilding cytoskeleton in endothelial cells and strengthens tight junctions between them[7]. Possibly, a similar effect is exerted by APC in colonocytes. No research has been done in this field as yet.

The only adverse effect of rhAPC administration is bleeding. It occurred in 2-3.8% of patients during 96 day infusion[8]. Despite significant necrotic lesions in the large bowel, no lower GI bleeding was observed in our patient during treatment. It seems that the benefit from the inhibition of intestinal wall inflammation, reduced bacterial translocation and decreased SIRS outweigh the potential risk of bleeding.

As already mentioned, the incidence of severe infections caused by *C. difficile* continues to increase, as well as several patients admitted to ICUs with this infection. The CDI treatment modalities alternative to metronidazole and vancomycin, such as nitazoxanide, rifaximin or intravenous immunoglobulins, are also not fully effective in all cases[4]. Based on the presented case, it would be sensible and reasonable to perform well-designed studies on rhAPC use in severe pseudomembranous colitis. This new agent was shown to be helpful in pseudomembranous colitis management, despite continued antibiotic therapy which is a major etiological factor of the disease and possibly to prevent bacterial translocation and subsequent SIRS and death.

The article, published in April 2022, presents a comprehensive investigation into the effects of Recombinant Human Activated Protein C (rhAPC) on inflammatory responses and coagulation in patients diagnosed with septic shock[9]. Although the primary focus of the study centers on septic shock, the findings offer intriguing insights that hold potential implications for the management of *E. coli* and *Clostridium* infections.

Within the study, a meticulous examination is conducted to elucidate the impact of rhAPC administration on diverse markers associated with inflammation and coagulation activation. By meticulously scrutinizing pro-inflammatory cytokine levels, coagulation parameters and endothelial cell activation markers, the researchers gain valuable insights into the complex mechanisms through which rhAPC influences these critical aspects.

The outcomes derived from this investigation demonstrate a noteworthy reduction in markers of inflammation and coagulation activation after rhAPC treatment. These compelling findings thereby suggest the promising utility of rhAPC as a potential therapeutic approach for managing infections caused by *E. coli* and *Clostridium*. Given the pivotal role played by inflammatory and coagulation responses in various types of infections, including those induced by *E. coli* and *Clostridium*, the observed effects of rhAPC on these key processes hold significant scientific and clinical implications.

It is important to emphasize that while the primary focus of the article revolves around the septic shock, the knowledge gleaned from the examination of rhAPC's effects on inflammatory responses and coagulation harbors broader implications for infectious conditions, such as those caused by *E. coli* and *Clostridium*. Nonetheless, it is imperative to acknowledge that further rigorous investigations, specifically tailored to explore the effectiveness of rhAPC in the context of *E. coli* and *Clostridium* infections, are warranted to comprehensively ascertain its therapeutic potential in these specific scenarios[9].

CONCLUSION

This case report sheds light on the challenging management of pseudomembranous colitis, especially when complicated by severe sepsis, where discontinuing antibiotics may not be feasible due to the need for effective treatment. The addition of Recombinant Human-Activated Protein C (rhAPC) to targeted antibiotic therapy, as recommended by the Surviving Sepsis Campaign in cases of septic shock with organ failure, demonstrated promising results in this unique

and complex case. The rhAPC's multifaceted properties, including its anti-inflammatory, antithrombotic and profibrinolytic effects, appeared to contribute to the patient's overall improvement and eventual recovery. This report underscores the need for further research to determine the optimal management approach for pseudomembranous colitis, particularly in cases where conventional antibiotic discontinuation is challenging. With the increasing incidence and severity of *Clostridium difficile* infections, alternative treatment strategies like rhAPC warrant thorough investigation. Additionally, exploring the potential applications of rhAPC in managing other infections with similar inflammatory and coagulation mechanisms, such as those caused by *E. coli* and *Clostridium*, holds significant promise and merits further exploration. While this case provides valuable insights, it is essential to acknowledge the need for controlled clinical studies to validate the efficacy and safety of rhAPC in the context of pseudomembranous colitis and related conditions. Such research endeavors will help refine treatment guidelines and potentially offer new therapeutic options for patients facing complex infectious challenges.

SIGNIFICANCE STATEMENT

This case report is significant because it explores a novel approach to managing the complex condition of pseudomembranous colitis with severe sepsis. It introduces the potential use of Recombinant Human-Activated Protein C (rhAPC), which offers hope for patients requiring ongoing antibiotic therapy while dealing with severe colitis and sepsis. This innovative treatment approach leverages rhAPC's multifaceted properties, addressing infection, inflammation and coagulation issues simultaneously. The report underscores the need for further research to validate this approach and highlights its broader implications for managing infections with similar mechanisms. Ultimately, it signifies a promising avenue for improving outcomes in complex infectious scenarios.

REFERENCES

1. Voth, D.E. and J.D. Ballard, 2005. *Clostridium difficile* toxins: Mechanism of action and role in disease. Clin. Microb. Rev., 18: 247-263.
2. Riddle, D.J. and E.R. Dubberke, 2009. *Clostridium difficile* infection in the intensive care unit. Infect. Dis. Clin. North Am., 23: 727-743.
3. Kenneally, C., J.M. Rosini, L.P. Skrupky, J.A. Doherty and J.M. Hollands *et al*., 2007. Analysis of 30-day mortality for *Clostridium difficile*-associated disease in the ICU setting. Chest, 132: 418-424.
4. Gerding, D.N., C.A. Muto and R.C. Owen Jr., 2008. Treatment of *Clostridium difficile* infection. Clin. Infect. Dis., 46: S32-S42.
5. Vincent, J.L., D.C. Angus, A. Artigas, A. Kalil and B.R. Basson *et al*., 2003. Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. Crit. Care Med., 31: 834-840.
6. Teke, Z., S. Sacar, C. Yenisey, A.O. Atalay, T. Kavak and E. Erdem, 2008. Role of activated protein C on wound healing process in left colonic anastomoses in the presence of intra-abdominal sepsis induced by cecal ligation and puncture: An experimental study in the rat. World J. Surg., 32: 2434-2443.
7. Levi, M. and T. van der Poll, 2007. Recombinant human activated protein C: Current insights into its mechanism of action. Crit. Care, Vol. 11. 10.1186/cc6154.
8. Hodder, R.V., R. Hall, J.A. Russell, H.N. Fisher and B. Lee, 2009. Early drotrecogin alpha (activated) administration in severe sepsis is associated with lower mortality: A retrospective analysis of the Canadian enhance cohort. Crit. Care, Vol. 13. 10.1186/cc7893.
9. Aysegül, T.A., E.K. Demirci, S.F. Ipek, H. Oflaz and M.A. Gerhard, 2022. Recombinant activated protein C (rhAPC) affects lipopolysaccharide-induced mechanical compliance changes and beat frequency of mESC-derived cardiomyocyte monolayers. SHOCK, 57: 544-552.