Findings that shed new light on the possible pathogenesis of a disease
or an adverse effect

Toxic megacolon from fulminant *Clostridium difficile* infection induced by topical silver sulphadiazine

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Summary

Pseudomembranous colitis and toxic megacolon (TM) are well-known complications of *Clostridium difficile* infections. Systemic antibiotic is considered as the major risk factor for the development of *C. difficile* colitis. However, topical antibiotics are rarely associated with the infection. As previously thought, the use of topical antibiotic is capable of systemic absorption in damaged and denuded skin; sufficient enough to suppress the normal bowel flora. Here, we present an unusual case of TM from *C. difficile* infection induced by topical silver sulphadiazine in a 60-year-old man with immune-bullous pemphigus vulgaris. The diagnosis is further complicated by the absence of diarrhoea as the initial presentation. Despite adequate medical and surgical intervention, the patient had an unfavourable outcome.

BACKGROUND

Clostridium difficile (*C. difficile*) is a Gram-positive, spore-forming organism usually transmitted by faecal to oral route.^{1–2} The mechanism of mucosal injury is related to its toxin-producing activity, capable of inducing severe pseudomembrane formation and mucosal destruction.^{1–3} The incidence and severity of *C. difficile* infection in the USA have been gradually increasing, with 3 million cases diagnosed each year.⁴ The economic burden of disease is overwhelming, with a 54% higher cost in hospitalisation as compared with those who did not have the infection.⁵ *C. difficile* infection ranges from asymptomatic carriers to pseudomembranous colitis (PMC), toxic megacolon (TM), perforation and death.⁶ The use of antibiotics is a well-known risk factor for the development of *C. difficile* infection.¹ However, the use of topical antibiotics such as silver sulphadiazine is rarely associated with the infection; with only one case reported throughout the English literature. Here, we present an unusual case of *C. difficile* infection induced by topical silver sulphadiazine in a patient with pemphigus vulgaris.

CASE PRESENTATION

A 60-year-old Caucasian man presented in the emergency department with complains of abdominal pain for the past 5 days. The patient stated that he began noticing the abdominal discomfort 5 days ago, which he described to be mostly localised to the lower abdomen as, sharp and constant with no alleviating or aggravating factors. The described pain had progressively gotten worst over the next few days, which prompted his visit to the emergency room. Associated symptoms include abdominal bloating and constipation. He denied any unintentional weight

loss, nausea, vomiting, diarrhoea, fever, chills, haematochezia and/or any recent sick contacts. Family history was non-contributory, including the absence of any malignancy or gastrointestinal disorder.

Medical history was significant for hypertension, chronic obstructive pulmonary disease, pemphigus vulgaris and chronic kidney disease. Home medications included oral prednisone, a fluticasone and salmeterol combination inhaler, tiotropium, clonidine and aspirin. Due to a recent worsening of his pemphigus vulgaris 8 weeks prior to the emergency room visit, the patient was prescribed 1% silver sulphadiazine cream to be applied on the affected areas of the skin twice daily. No history of systemic antibiotic use was reported over the last 3 months.

Physical examination revealed a well-nourished man in mild distress secondary to abdominal pain. Vital signs were significant for tachycardia of 131 beats per minute. General examination revealed the presence of multiple blisters on the bilateral extremities, some of which appeared to be crusting. Abdominal examination revealed a distended abdomen, with diffuse tenderness to palpation. Bowel sounds were present in all four quadrants of the abdomen, but appeared to be diminished. Rectal examination did not reveal any impacted stools, rectal masses and/or visible blood. Laboratory evaluation was remarkable for a leucocytosis of 17 000/mm³, with a significant bandemia of 28%. Initial lactate level was 1.2 mmol/l, and blood urea nitrogen and creatinine levels were 50 and 1.9 mg/dl, respectively. Subsequent CT of the abdomen and pelvis revealed a considerable diffuse hypodense thickening of the colon with extensive stranding of the peri-colonic fat, suggestive of pancolitis (figure 1).

Figure 1 Computed axial tomography of the abdomen and pelvis. Note the diffuse hypodense thickening of the colon with extensive pericolic fat stranding (arrow).

Stool for *C difficile* was subsequently sent, which later came back positive for both toxin A and toxin B.

The patient was hydrated and kept nulla per os (NPO) overnight. Blood cultures were drawn, and the patient was started on metronidazole and oral vancomycin; a regimen commonly used for the treatment of *C difficile* colitis.

Over the next 3 days, the patient started to develop loose watery stools on several occasions, associated with fever, chills and worsening abdominal pain. Along with his worsening renal function, he became tachypnoeic and was subsequently intubated. Due to the worsening abdominal pain, a repeat CT scan of the abdomen was performed, which revealed prominent diffuse thickening of the colon with pericolic inflammatory changes and signs of TM (figures 2 and 3). A repeat laboratory evaluation revealed an elevated leucocyte count of 34 600/mm³ and lactate level of 2.5 mmol/l. An immediate surgical evaluation was requested, and the patient underwent a subtotal colectomy with ileostomy. Histopathological evaluation of the specimen revealed extensive PMC (figures 4 and 5).

OUTCOME AND FOLLOW-UP

The patient remained hypotensive after the procedure despite adequate antibiotics and blood pressure support. Further hospital course was complicated by acute respiratory distress syndrome, persistent hypotension and multi-organ failure, which eventually led to the patient's demise on day 12 of admission.

DISCUSSION

PMC is a well-described complication of *C difficile* infection. It is characterised pathologically by the formation of discrete plaque-like lesions of the colon; believed to be

induced by the overgrowth of toxigenic strains of *C difficile* organism.¹ PMC if left untreated can rapidly progress to TM, perforation and death.⁶ TM in PMC has an estimated incidence of 0.3–3% with death rate ranging from 38% to 80%.^{7,8}

The pathogenicity of *C difficile* infection is not related to the organism itself, but rather to the production of

Figure 2 Abdominal x-ray showing multiple dilated bowel loops.

Figure 3 Repeat CT of the abdomen, note the worsening pancolitis with dilated bowel loops (arrow).

various toxins. Toxin A and toxin B disrupts the actin cytoskeleton of the interstitial epithelial cells by the uridine diphosphate—glucose-dependent glucosylation of proteins.^{1 2 6 9} These toxins lead to the induction of inflammatory mediators, namely interleukin 8, substance P, tumour necrosis factor- α and macrophage inflammatory protein 2, which subsequently leads to fever, multiorgan failure, TM and perforation.⁶ The role of binary toxin, initially described in 1988, is uncertain; with reports describing its association with the more virulent NAP1/B1/027 strain.^{2 10}

The clinical triad for *C difficile* colitis is fever, abdominal pain and watery diarrhoea.¹¹ The absence of diarrhoea, however, should not waiver the diagnosis of *C difficile* colitis.³ It has been suggested that as much as 30% of patients will not present initially with diarrhoea.

Furthermore, localised colitis in the caecum and the right colon will result in little or no diarrhoea at all.¹²

The greatest risk factor for the development of *C difficile* colitis is the suppression of gut flora from the use of systemic antibiotics. Almost all types of antibiotics have been associated to cause *C difficile* colitis, the most common of which includes clindamycin, penicillins, cephalosporins and fluoroquinolones.^{13 14} Although rare, topical antibiotics have also been implicated to cause *C difficile* infection. Several reported cases of topical clindamycin for the treatment of acne resulted in the development of *C difficile* PMC.^{15 16} Furthermore, experimental studies on animals have also demonstrated the induction of colitis after topical application of antibiotics.¹⁷

Figure 4 Gross specimen of the resected colon from a 60-year-old man with severe pseudomembranous colitis showing multiple, widely distributed pseudomembranes.

Figure 5 Microscopic specimen of the resected colon. Note the collection of fibrin and polymorphonuclear cells along with karyorrhectic debris (A), adherent to damaged mucosa (B).

Topical silver sulphadiazine has been widely used as an effective topical agent in burn patients since the 1960s.^{18–19} Like other heavy metals, silver is toxic to microbes, with a broad bactericidal action. The mechanism of action of silver involves the poisoning of the components within the electron transport system and the DNA functioning of cells.^{18–20} In recent years, silver sulphadiazine and silver-containing hydrophobic dressings have been used as an adjunct therapy for immune-bullous diseases, including pemphigus vulgaris.^{21–22} Together with its use, comes with the increase risk of side effects, namely silver poisoning, leukopaenia, renal failure and *C difficile* infection.^{19–23–24} The first reported case of topical silver sulphadiazine-associated *C difficile* infection was in 1998 by Jennings and Hanumadass²⁴ involving a patient with severe burns. Our case is the second to be reported in the English literature.

Topical silver sulphadiazine is believed to be absorbed in the system in higher quantities than expected. In a study by Wan *et al*,²³ burn patients receiving the topical antibiotic demonstrated a considerable increase of silver content in the blood within 6 h after the application of silver sulphadiazine cream; more than 50-fold higher than the normal blood concentration of silver. Once in the bloodstream, levels continue to increase over the next 48 h, reaching its plateau in 3–4 days before it is excreted in the faeces.^{19–23} The sulphadiazine portion of the compound is metabolised in the liver and excreted in the urine.¹⁹ In a similar study by Sano *et al*¹⁹ on experimental animals also demonstrated an increase in the absorption of silver on burned-denuded skin. However, no increase was noted on normal skin of experimental animals. This observation might explain the possible risk of *C difficile* PMC in patients with chronic use of silver sulphadiazine cream by altering the gut flora, similar to the use of systemic antibiotics.

The patient's long-term use of silver sulphadiazine cream confounding with the use of systemic steroids may have contributed to the development of fulminant *C difficile* infection. The absence of recent systemic antibiotic use and the absence of diarrhoea during the initial presentation of the case discussed, further complicated the diagnosis of *C difficile* colitis. The absence of diarrhoea seemed to have no bearing on the severity of the disease condition and should not waiver early aggressive therapy for *C difficile* colitis.

Although no reported cases of steroid use masking the symptoms of *C difficile* infection are present, the use of steroids in patients with fulminant inflammatory bowel disease has been reported. Patients with inflammatory bowel disease using systemic steroids have been reported to have masked signs of peritoneal irritation, perforation and abscess formation.^{25–28} Furthermore, the role of steroids masking an infectious diarrhoea such as *Campylobacter* colitis have also been reported.²⁹ In a study by Flegel *et al*³⁰ and Mahida *et al*,³¹ epithelial cells infected by *C difficile* organisms cause the release of interleukin-8 and macrophage inflammatory protein-2.³² These pro-inflammatory mediators cause the submucosal macrophages, monocytes and dendritic cells to disseminate an inflammatory cascade with further release of pro-inflammatory cytokines. The combined action of cytokines and histamine subsequently increases the

permeability of the vascular endothelium causing fluid leakage and the symptomatic profuse watery diarrhoea seen with *C difficile* infection.³² On the other hand, the role of steroids in suppressing pro-inflammatory cytokines and monocyte migration might explain the possibility of masking the usual diarrhoeic symptoms of *C difficile* infection, similar to the case discussed.^{33–34}

Topical antibiotics, such as silver sulphadiazine, have been considered relatively safe for the treatment of different skin infections; however, special consideration on the risk for developing *C difficile* colitis must be considered. Several studies have demonstrated the systemic absorption of topical antibiotics and the primary excretory mode of silver in the colon might play a significant role in the suppression of the gut flora and the subsequent overgrowth of *C difficile*-producing organism. Clinicians should have heightened suspicion of *C difficile* infection, especially in immunocompromised patients with long-term topical antibiotic use and gastrointestinal complaints.

Learning points

- ▶ Topical antibiotics can be absorbed in the system in higher quantities than expected.
- ▶ The use of topical antibiotics such as silver sulphadiazine might predispose patients for the development of *Clostridium difficile* infection.
- ▶ *C difficile* colitis can develop even in the absence of diarrhoea.
- ▶ A standardised scoring system for the predictors of fatal outcome in *C difficile* colitis must be developed, to help clinicians decide the appropriate time for surgical intervention prior to the development of toxic megacolon.
- ▶ The use of steroids might play an important role on masking the usual diarrhoeic symptoms of *C difficile* infection.

Competing interests None.

Patient consent Obtained.

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