HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2022; 9(2):1189-1195

UDC: 616.98-085-06:578.834]-055.26

doi:10.5937/hpimj2202189M

Case Report

Toxic Megacolon After Irrational Antibiotic Treatment of Pregnant Patient With Covid 19: Case Report

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SUMMARY

Introduction: Optimal management of toxic megacolon as a consequence of Cl. difficile colitis is still matter of controversy, as well as timing of available therapeutic modalities. In this article we report a case of severe C. difficile colitis associated with toxic megacolon in a pregnant patient with Covid 19, who was successfully treated conservatively.
Case Report: A 33-years old pregnant woman contracted SARS-CoV-2 in the 32nd week of pregnancy. She was admitted to regional hospital and treated extensively by wide-spectrum antibiotics. After the delivery she developed severe form of Cl. difficile colitis with toxic megacolon. In spite of severe clinical picture, the patient was treated conservatively, with high initial oral doses of vancomycin, with subsequent tapering. The outcome of the treatment was complete recovery and colonic functions were regained completely.
Conclusion: In conclusion, our case shows that in younger patients, who were fit before occurrence of Cl. difficile colitis and toxic megacolon, conservative therapy should be tried as long as possible before turning to colectomy, since chances for cure without surgery are considerable.

Keywords: CCl. Difficile Colitis, Toxic Megacolon, Vancomycin

INTRODUCTION

Toxic megacolon is life-threating disease and may be defined as a nonobstructive partial or pan colonic dilatation in excess of 6 cm with signs of systemic toxicity [1,2].

Leading cause of toxic megacolon is Inflammatory bowel disease, but it could be consequence of Clostridium difficile infection, too [3]. Incidence of toxic megacolon after colitis induced by Clostridium difficile is relatively low and ranges from 0.4% to 3%, but the mortality rate is very high, between 38% and 80%, mostly due to colonic perforation followed by peritonitis, septic shock and multiple organ dysfunction[4,5,6]. In hospital settings main reason for Cl. Difficile infection (CDI) is prolonged treatment of patients with broad-spectrum antibiotics. Current COVID 19 pandemics has contributed to this problem

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indirectly, through overzealous administration of antibiotics to patients with COVID 19 and pneumonia, since it is difficult in clinical practice to differentiate between viral and bacterial origin of pneumonia, especially in resource-poor settings [7].

Although clindamycin, cephalosporins and fluoroquinolones are antibiotics the most frequently associated with C. Difficile infection, other broad-spectrum antibiotic are followed by certain percentage of Cl. Difficile cases, too [8]. Toxins of C. difficile induce release of proinflammatory cytokines into the colon wall which further increase permeability of blood vessels and cell necrosis [9]. Mourelle et al showed induction of inducible nitric oxide (NO) synthetase in the muscularis propria of patients with toxic megacolon [10]. Increased production of NO leads to inhibition of smooth muscle tone and colon becomes dilated [11]. Sudden stopping of diarrhea due to ileus, rapid abdominal distension, abdominal pain and tenderness, tachycardia and hypotension in patients diagnosed with CDI are key signs pointing to emergence of toxic megacolon [12]. The diagnosis of toxic megacolon has to be radiologically confirmed. Computerized Tomography (CT) of abdomen may show at least 6 cm wide dilatation of colon, wall thickening, distortion of haustral folds, and ascites [13]. Optimal management of toxic megacolon is still matter of controversy, as well as timing of available therapeutic modalities [14]. We found only one case report with association toxic megacolon in Covid 19 patient and they tried with antibitiocs but main therapy was a surgery,because patient had a perforation of colon [15].

In this article we report a case of severe C. Difficile colitis associated with toxic megacolon in a pregnant patient with Covid 19, who was successfully treated conservatively.

CASE REPORT

The patient was a 33-year-old woman with hypothyroidism on tablets levothxroxine-natrium (Euthyrox®, Merck Healthcare KgaA) 100 mcg / daily, without allergy and previously operation, in well health condition, who in the 32nd week of pregnancy contracted SARS-CoV-2.

She was admitted to regional hospital and treated with broad spectrum antibiotics from the first day of admission cefpodoxime (Tridox®, Alkaloid AD Skoplje) 200 mg / daily per os. On 11th day of hospitalization, when patient was in 34nd week of pregnancy, an elective Cesarean section was performed and healthy child was born, APGAR score 9, without evidence of SARS-CoV-2 infection, in next period. Five days after the section, mother and child were discharged from the hospital and mother did not breastfeed a child by recommendation of a physician. However, two days later she was admitted again due to occurrence of frequent stools, fever and malaise. The laboratory results during admission showed haemoglobin (110-180 g/L) level of 113 g/l, amylase (40-140 U/L) 5944 U / L, albumin (41-51 g/L) 22 g/l, C reactive protein (0-5 mg/L) 210 mg/l, and microbiological examination of stool was positive for Clostridium difficile. The high amylase values we described as part of systemic inflammatory response syndrome. On the emergency Multi-Slice Computer Tomography (MSCT) of the abdomen, there was a whole postcontrast enhancement of the mucosa, edema of the submucosa, and of the muscle layer. The external contours were unclear, while ascites and edema of peritoneal and subcutaneous fat (anasarca) were present. Pleural effusions were seen bilaterally in the basal parts of the lung parenchyma, up to 4.5 cm thick on the right and 5 cm on the left, with compressive atelectasis of the parenchyma.

After a few days of antibiotic therapy with cephalosporins and fluoroquinolones, the patient was transferred to a tertiary institution where the laboratorian results showed gradual decrease (during the first 20 days) of haemoglobin (110-180 g/L) from 147 g/l to 76 g/l, C reactive protein (0-5 mg/L) dropped to 84 mg/l, procalcitonin (0-0.1 ng/ml) was 0.93 ng/ml, amylase (40-140 U/L) was 338 U/ l, albumin (41-51 g/L) was 22 g/l, D-dimer (0-0.5 μ/mL) was 4.8 μ/mL, and urine culture was positive for Klebsiella spp. Typical features megacolon of were seen on the repeated MSCT: Diameter of caecum was 66 mm, and that of transverse colon and rectum 68 mm and 70 mm, respectively. The content of the colon was liquid, its wall edematous and mucosa intensely stained after administration of contrast. The small intestine was also moderately distended, with liquid content, and the mucosa was moderately stained after giving contrast to the patient.

The patient was treated with vanc-

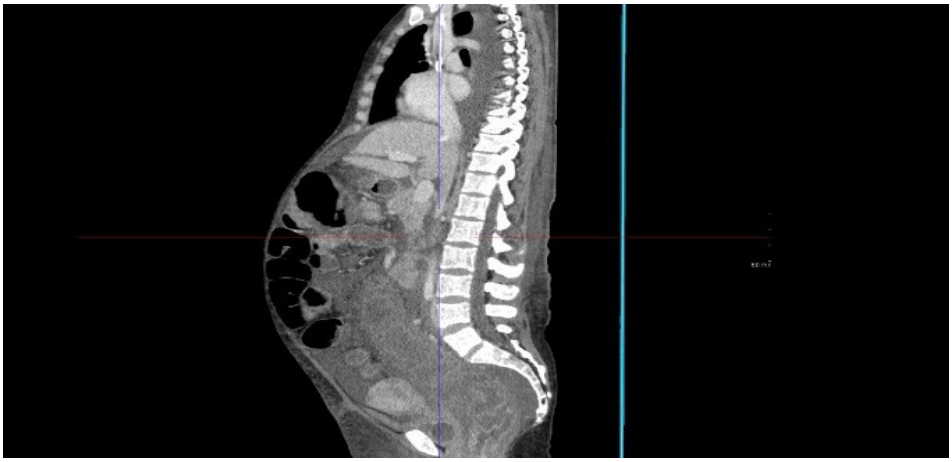

Figure 1. MDCT in sagittal plane, Multiplanar (MPR reconstruction-saggital section)distension of the colon just below the anterior wall.

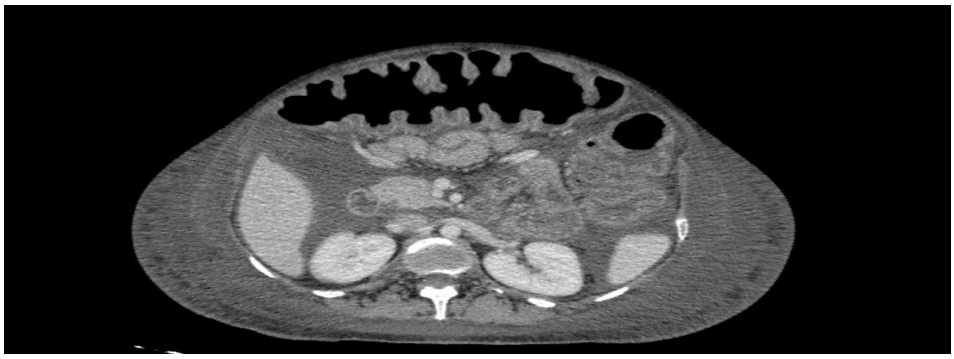

Figure 2. MDCT- axial section at the level of the transverse part of the colon which is extremely dilated.

omicin (Voxin®, Vianex S.A.-Plant C) 1 g at 24^{h} administered both orally and by an enema, the ampules metronidazole (Orvagil®, Galenika AD Beograd) 500 mg at 8^{h} was given intravenously, and the following drugs were also added intravenously: corticosteroids (metylprednisolon Lemod®-Solu Hemopharm AD Vršac 40 mg/ ml intravenously at 24^{h}) , human albumin (Albutein 20% Instituto Grifols S.A. 200 g/L intravenously at 8^{h}), diuretics (furosemid Lasix® Opella healthcare international sas 40 mg at 24^{h} per os), neostigmin-metilsulphat (Neostigmine/Cooper, Cooper S.A. 2.5 mg/ml at 24^{h} intramuscular) and packed red cells transfusions with 3 units (one unit 250 mL), haemoglobin (110-180 g/L) transfusion trigger was 80 g/L. She was not treated surgically due to low parameters of inflammation, C reactive protein dropped to 64 mg/l (0-5 mg/L) , preserved peristalsis and the absence of abdominal pain. However, during this period, nearly 2 weeks of hospitalization the patient remained febrile with maximum 38 degrees Celsius (C^{o})/ 100.4 degrees Fahrenheit and never less from 37.3 C^{o}/ 99.32 degrees Fahrenheit.

After vital functions of the patient became stable, temperature was 37.5 C^{o}, CRP dropped to 45 mg/l (0-5 mg/L), blood pressure was 100/60 mmHg, patient was transferred to the internal medicine department. The abdomen was extremely enlarged, with circumference of 111 cm at the level of umbilicus. The fever persisted, and the patient developed cellulitis of the lateral parts of anterior abdominal wall. The laboratory showed low haemoglobin (110-180 g/L) from 77 mg/l to 95 mg/l, D-dimer 2,87 μ/mL (0-0.5 μ/mL), albumin (41-51 g/L) from 26 g/l to 39 g/l, C reactive protein (0-5 mg/L), gradually dropped to 39 mg/l, and then to 6.9 mg/l , amylase (40-140 U/L) and procalcitonin (0-05 μg/L) became normal. The patient was treated additionally with parenteral vancomycin, while oral administration of vancomycin (Voxin®, Vianex S.A.-Plant C) and ampules metronidazole (Orvagil®, Galenika AD Beograd) 500 mg at 8^{h} was continued. Serum levels of vancomycin (Voxin®, Vianex S.A.-Plant C) were monitored to prevent toxicity. The signs of cellulitis gradually abated, however repeated MDCT showed persistent signs of colonic inflammation: the wall of large intestine was up to 3 cm thick in some parts due to extensive edema, and several inclusions of gas were seen in submucosa. General condition of the patient was improved little by little, as well as her stools. Antibiotic therapy with

intravenous vancomycin and oral metronidazole was discontinued after 3 weeks, and oral vancomycin (Voxin®, Vianex S.A.-Plant C) 1 g at 24h was continued with tapering doses for further 5 weeks.

The patient was discharged after 46 days of hospitalization for further home treatment when an additional MSCT showed signs of mild intestinal distension. She continued taking oral vancomycin (Voxin®, Vianex S.A.-Plant C) at home with tapered doses until 8 weeks from the beginning of oral vancomycin (Voxin®, Vianex S.A.-Plant C) ensued. After 1.5 months at home, the patient came for a check-up in good health.

DISCUSSION

Diagnosis, and especially therapy of clostridial infection is a problem at any level of the health system organization.

The greatest effect in therapy would be achieved by complete exclusion of antibiotic therapy in the patient, in order to allow spontaneous recovery of the intestinal flora and restoring the balance between pathogenic and non-pathogenic strains. Such an approach, usually is not possible in a practice, because, often, these patients have multiple associated infections, systemic infections or are in a critical general health condition, and therefore, treatment with antibiotics is necessary.

According to the recommendations, metronidazole or vancomycin should be administered orally as the first line drug treatment, although, metronidazole may also be administered intravenously, especially in hospitalized patients, in critical condition. According to some authors, possible presence of adynamic ileus in patients during the postoperative course can significantly affect the distribution and absorption of orally administered drug, and therefore, vancomycin enema is often given as an additional therapy [16].

Vancomycin should be included in the treatment of the first relapse of CDI only if there is a return of symptoms of the disease associated with clinical parameters that indicate a severe form of the disease (if the patient has severe leukocytosis, or hypotension and renal failure). Each relapse of the disease should be treated primarily with vancomycin, with long-term gradual dose tapering, or with the use of pulse doses over a long period of time. Some of the authors recommendedthe following tapering regimen: during the first two weeks of therapy, vancomycin should be administered in a dose of 1 g daily, divided into 4 doses, then 500 mg divided into two doses over the next 7 days, then 125 mg in a single dose for another 7 days. After that, the therapy should be applied in a dose of 125 mg, but first on every other day for a total of 8 days, and then on every third day for another two weeks. In general, there is a number of therapeutic approaches with gradual dose reduction, and further research should confirm the superiority of one of these approaches [17,18]. However, If these treatment regimens do not lead to a cure, treatment with oralrifaximineis sometimes suggested [19].

There is small number of studies examining the efficacy of ramoplanin and nitazoxanide in relapsed CDI. A lower degree of resistance was observed to ramoplanin compared to vancomycin. On the other hand, nitrazoxanid has shown similar efficacy as the drugs used so far for CDI but additional studies need to confirm the safety of its use [20,21]. However these two drugs do not have marketing authorization for treatment of Cl. Difficile colitis, yet. In the treatment of recurrent forms, fidaxomicin can be used. Fidaxomicin is more effective than vancomycin in terms of the number of recurrent cases. It has similar properties as vancomycin. Its absorption from the digestive tract is minimal , so the possibility of side effects is low. It also has a minimal bactericidal effect on the remaining microorganisms that are part of the normal intestinal flora [22,23].

Studies have shown that despite the practice of excluding proton pump inhibitors (PPIs) and H2 blockers - from CDI therapy, relapse is only affected by infection-specific drugs [24]. Also, using additional antibiotics in order to control other and systemic infections that are concomitant with CDI, is associated with prolonged duration of diarrhea and a greater number of recurrent forms of CDI [25].

A vaccine that can prevent recurrent forms of CDI has been developed. It is a toxoid vaccine that allows the production of protective antibodies to the toxin Clostridium difficile : toxins A and B. Recent recommendations include using of intravenous immunoglobulins (IVIG) in CDI, which is mainly based on neutralization mediated by antibodies to toxin

A, although antibodies to toxin B have an additive effect [26,27,28]. Up to date, it has not been proven that the use of probiotics can prevent the occurrence of recurrent forms of CDI. Fecal transplantation is one of newer methods used in patients with severe clinical picture and in those in whom all other treatment modalities were ineffective. It can also be used in patients with toxic megacolon within the CDI, who are candidates for surgical treatment. The stool of a healthy donor is inserted through a catheter into the lower or upper part of the digestive tract. In this way, it can stimulate the restoration of the normal flora of the patient's digestive tract [29].

In patients with CDI-induced megacolon who did not develop additional complications, mortality is about 15%. This mortality increases if the patient develops more severe complications over time, such as ischemia and perforation of the intestinal wall [30].

The mortality of patients with CDI toxic megacolon who were subjected to total colectomy before occurence of perforation, is significantly lower compared to those who were operated after the large bowel perforation [31,32]. Besides, surgery significantly reduces mortality if performed before development of septic shock [33].

Of course, it is necessary to think about the Oligvie syndrome as differential diagnosis, but Ogilvie syndrome usually does not present with signs of systemic toxicity, with similar CT finding as toxic megacolon [34].

In our patient we combined the use of metronidazole as the first treatment line and vancomycin in patients with severe infection, the main reason is better efficacy compared to the use of only one antibiotic and less chance for resistent on both antibiotics in similar time [34,35].

CONCLUSION

In conclusion, our case shows that in younger patients, who were fit before occurrence of Cl. difficile colitis and toxic megacolon, conservative therapy should be tried as long as possible before turning to colectomy, since chances for cure without surgery are considerable. Total colectomy bears significant morbidity by itself, therefore any chances to avoid it without endangering the patient's life should be taken.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Toksični megakolon posle iracionalne primene antibiotika u lečenju trudnice sa Covid-om 19: prikaz slučaja

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KRATAK SADRŽAJ

Uvod: Optimalno upravljanje toksičnim megakolonom kao posledicom Cl. difficile kolitis je još uvek predmet kontroverzi, kao i vreme kada su dostupni terapijski modaliteti. U ovom članku izveštavamo o slučaju teškog kolitisa C. difficile povezanog sa toksičnim megakolonom kod trudnice sa Covid-om 19, koja je uspešno lečena konzervativno.

Prikaz slučaja: Trudnica stara 33 godine zarazila se SARS-CoV-2 u 32. nedelji trudnoće. Primljena je u regionalnu bolnicu i intenzivno lečena antibioticima širokog spektra. Nakon porođaja razvila je teški oblik Cl. difficile kolitis sa toksičnim megakolonom. I pored teške kliničke slike, pacijent je lečen konzervativno, visokim početnim oralnim dozama vankomicina, uz naknadno smanjivanje. Ishod lečenja je bio potpuni oporavak i potpuno su vraćene funkcije debelog creva.

Zaključak: U zaključku, naš slučaj pokazuje da kod mlađih pacijenata, koji su bili u formi pre pojave Cl. difficile kolitisa i toksičnog megakolona, konzervativnu terapiju treba pokušavati što je duže moguće pre nego što se pređe na kolektomiju, pošto su šanse za izlečenje bez operacije znatne.

Ključne reči: *Cl. difficile* kolitis, toksični megakolon, vankomicin

Received: May 16, 2022
Accepted: June 29, 2022