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Severe *Clostridium difficile* infection with extremely high leucocytosis complicated by a concomitant bloodstream infection caused by *Klebsiella pneumoniae* after osteomyelitis surgery: A case report

Iveta Golubovska^{a,d,*}, Dace Vigante^b, Martins Malzubris^b, Luize Raga^b, Sergejs Isajevs^{c,d}, Aleksejs Miscuks^{a,d}

^a Department of Anesthesiology, Hospital of Traumatology and Orthopedics, Riga, Latvia

^b Department of Joint and Bone Infections, Hospital of Traumatology and Orthopedics, Riga, Latvia

^c Joint Laboratory for Microbiology and Pathohistology, Hospital of Traumatology and Orthopedics, Riga, Latvia

^d Faculty of Medicine, University of Latvia, Riga, Latvia

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ABSTRACT

INTRODUCTION: *Clostridium difficile* is one of the most common healthcare-associated infections. Pseudomembranous colitis is a serious complication of *Clostridium difficile* infection (CDI) after septic surgery and antibacterial therapy. A sudden white blood cell (WBC) count increase and extremely high leucocytosis may be a predictor of a poor outcome.

PRESENTATION OF CASE: A 77 years old male was hospitalised because of lower leg osteomyelitis and was operated. He received antibacterial treatment with Cefazolin for three days and then developed a high WBC count. The course of the disease was fulminant, with a rapid increase in the WBC count up to 132,000/mm³ and a septic shock, and required cardiovascular and ventilatory support. The patient was started on intravenous Metronidazole (500 mg every eight hours) and oral Vancomycin (500 mg every six hours). The patient's condition gradually improved over a period of six days. Then a hyperthermia above 39 degrees Celsius, hypotension and painful abdominal bloating developed, and the WBC count peaked to 186,000/mm³. The blood cultures were positive for *Klebsiella pneumoniae*. The patient died.

DISCUSSION: In our case, we describe a community-onset, healthcare-facility-associated, severe CDI complicated by a blood stream infection. The administration of oral Vancomycin, which is highly active against the intestinal flora, could have been responsible for the persistence and overgrowth of *Klebsiella pneumoniae*.

CONCLUSIONS: Severe CDIs after orthopaedic surgery and antibacterial treatment complicated by the development of nosocomial infection significantly worsen the prognosis of the disease. Careful consideration of antibacterial therapy and early symptom recognition may help prevent catastrophic events.

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1. Introduction

Clostridium difficile infection (CDI) is one of the most common healthcare-associated infections, with high morbidity and mortality rates. *Clostridium difficile* is a spore-forming, anaerobic, Gram-positive bacterium. *Clostridium difficile* toxins can cause severe complications, including non-stopping diarrhoea, pseudomembranous colitis (PMC), toxic megacolon, perforations of the colon and sepsis [1–4].

A sudden increase in white blood cell (WBC) count coinciding in asymptomatic patients who receive antibacterial therapy after

septic surgery may be a predictor of *Clostridium difficile*-associated diarrhoea, while extremely high leucocytosis may be a predictor of a poor outcome [5].

Meta-analyses suggest that exposure to several antibiotic categories, including clindamycin, fluoroquinolones, cephalosporins, penicillins, macrolides and sulphonamides/trimethoprim, is associated with an increased risk of CDI in adults [5].

Severe CDIs are often complicated by the development of nosocomial bloodstream infections (BSIs) that significantly worsen the prognosis of the disease. Candida or enteric bacteria for the most part cause BSIs, and the mortality rate associated with this infection is very high – up to 50 % [6–10].

The aim of this paper is to report a fatal case of orthopaedic surgery complicated by *Clostridium difficile* infection and bloodstream *Klebsiella pneumoniae* infection.

* Corresponding author at: Department of Anesthesiology and Intensive Care, 12 Dunties Street, LV-1005, Riga, Latvia.

E-mail address: iveta.golubovska@tos.lv (I. Golubovska).

The case report was written according to SCARE guidelines [11,12].

2. Presentation of case

A 77 years old male with a medical history of hypertension, atherosclerosis, ischaemic attacks and chronic kidney disease was admitted at the ICU because of an altered mental state and cardiovascular collapse. The patient was afebrile and stuporous, with a pulse rate of 110 bpm and white blood cell count of $100,440/\text{mm}^3$. The level of haemoglobin was 73 g/L and of C-reactive protein – 251 mg/L. Urinalysis was unremarkable.

The patient was hospitalised six days earlier due to left tibia chronic osteomyelitis that had developed after osteosynthesis with a locked intramedullary nail seven years ago. The patient presented with stable infected pseudarthrosis, bone resorption around the nail and locking screws, abscess in soft tissue and a healed fibula fracture. The patient has not had any surgical treatment due to infection before, except abscess incision. He had not been taking any prescription antimicrobial agents at home. Two days after admission the patient was operated. Under general anaesthesia in supine position, using a tourniquet on the thigh, the following steps were performed: wound revision, implant removal, bone channel reaming, rinsing and antibiotic-loaded cement nail and spacer implantation. Surgery was performed by a trauma surgeon specialising in bone and joint infections. Analyses from the bone infection site revealed Methicillin-sensitive *Staphylococcus aureus*. The patient received antibacterial therapy with Cefazolin 1 g every six hours for three days after the surgery and then suddenly developed an elevated WBC count of up to $54,000/\text{mm}^3$ without any concomitant symptoms.

The course of the disease was fulminant, with a rapid increase in the WBC count up to $133,420/\text{mm}^3$ and a septic shock. Oro-tracheal intubation and fluid resuscitation were performed, followed by intravenous norepinephrine and cardiovascular and ventilatory support. Flow cytometry was done for the purpose of differential diagnosis, to exclude a malignant haematological disease. Blood culture was negative. Promisingly, a positive *Clostridium difficile* A and B toxin test was obtained from stool. The patient was started on intravenous Metronidazole (500 mg IV every eight hours) and oral Vancomycin (500 mg every six hours).

Following five days of treatment the patient's condition gradually improved. Then, suddenly, a hyperthermia above 39 degrees Celsius, shivering, hypotension and painful abdominal bloating developed. The WBC count peaked to $186,230/\text{mm}^3$ (Table 1). The rapidly developing, unstable haemodynamics required increasing doses of vasopressors. An urgent CT scan was performed, and neither open air, nor fluid were found in the abdomen. The consulting abdominal surgeon refused surgical intervention. The patient died 20 h after the beginning of the episode concerned. The microbiological blood cultures collected before death showed *Klebsiella pneumoniae* resistant to some antibacterial drugs, such as cephalosporins.

A post-mortem was done, and the findings were as follows: *Clostridium difficile* pseudomembranous colitis, local purulent-fibrinous peritonitis, septicaemia with local foci (in the heart, spleen, lungs, kidneys) (Figs. 1–4).

3. Discussion

A prior antibiotic treatment is the most important risk factor for the development of CDI. The antibiotic treatment disrupts the normal colonic microbiota, making individuals susceptible to CDI [13].

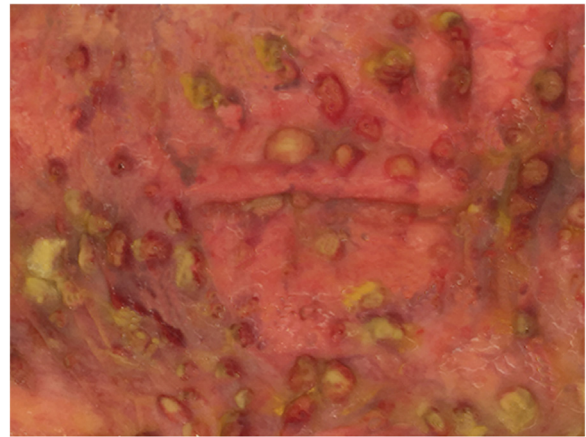


Fig. 1. Representative image of the colon descendent surface obtained during the post-mortem examination.

Data on the antibiotic therapy within the previous 30 days as well as other risk factors for the multidrug-resistant organisms were gathered from the discharge letter and summary from the previous hospitalisation in other facilities. These data were negative [1–3,14].

We can assume that this patient was an asymptomatic carrier since the previous hospitalisation episodes, despite the fact that the last episode was five years ago [14,15].

Typically at our surgical wards we start treatment with oral Metronidazole if a patient has unexplained diarrhoea, leucocytosis and subfebrile temperature, and we start empirical treatment with intravenous Metronidazole (500 mg IV every eight hours) and oral Vancomycin (125–500 mg every six hours) at the Intensive Care Unit when the symptoms worsen [5].

The more rapidly the life-threatening symptoms occur, the more motivated clinicians become to initiate early and intensive empirical treatment [16].

The recommended treatment for first recognised episodes is stratified based on the severity (mild to moderate or severe) of CDI assessed by WBC count (above or below $15,000/\text{mm}^3$), serum creatinine level (1.5 times the pre-morbid level), hypotension or shock, ileus and megacolon, which are characteristic of a severe, complicated (a.k.a. fulminant) CDI [17].

We followed the recommendation for an initial fulminant episode with hypotension and shock: Vancomycin 500 mg four times a day via nasogastric tube and Metronidazole 500 mg every eight hours intravenously. Gastric bypassing was applied [5].

Neutrophils are the first cells recruited to the colon in response to a CDI, and the neutrophil response is believed to be a determinant of the severity of the disease. Autopsy showed extremely dense leukocyte infiltration in tissues.

The production of neutrophil growth factor in the inflamed tissue facilitates the initial migration of neutrophils from the bone marrow into peripheral circulation and the recruitment of neutrophils to the CDI site. Neutrophil-mediated inflammation and neutrophil activity itself can lead to immune-mediated damage of host tissues [18].

The following parameters had the most evidence to support their use as markers of risk for mortality in CDI when assessed at or near the time of diagnosis: age, most likely with a cut-off between >65 and 75 years; WBC, with a cut-off of $>20,000/\text{mm}^3$; serum creatinine, possibly with a cut-off of $>200 \text{ mmol/L}$; and serum albumin, most likely with a cut-off of <25 to 35 g/L [17].

The impact of healthcare-associated bloodstream infections (BSIs) in complicating CDIs is huge [10]. The alterations occurring

Table 1
Laboratory investigations in the course of the disease.

Day	WBC /mm ³	CRP mg/L	Microbiology	Lactate level mmol/L	Albumin level g/L	Serum creatinine mkmol/L	GFR mL/min/1.73 m ²	SOFA Score points
0	54,840	154				173	35	
1 (admitted at ICU)	100,440 132,420	251	<i>Cl. Diff.</i> A and B toxins positive Blood culture negative	1.2	22.6	251 259	23 22	15
2	116,580	223.9		1.5		274	20	
3	83,870	125.4		2.3	21.8	219	27	
4	59,260	150.7		Low		162	38	
5	55,290	131.5		1.2	21.8	132	48	
6	70,560	69.4				118	55	
7	63,890	28.4			23.4	86	79	
8	186,230	80.3	<i>Kl. pneumoniae</i>	3.0		131	48	12

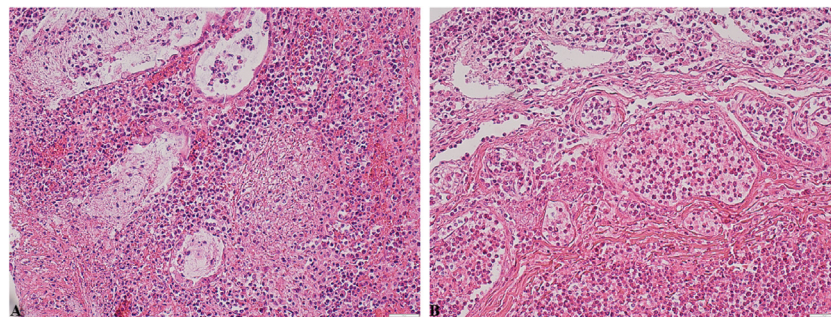


Fig. 2. Representative photomicrographs demonstrate extensive neutrophil infiltration in the lung tissue and blood vessels. The haematoxylin-eosin staining method, magnification ×100 (A), magnification ×200 (B).

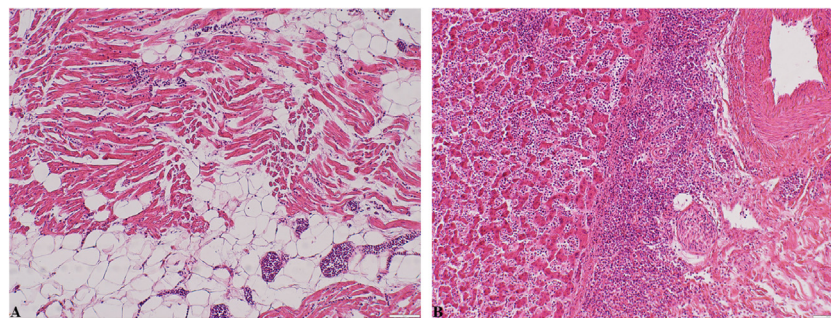


Fig. 3. Representative photomicrographs demonstrate: (A) the myocardial tissue with extensive neutrophil infiltration among cardiomyocytes and in blood vessels; (B) extensive neutrophil infiltration in the kidney tissue, mostly among the tubules and in small blood vessels. The haematoxylin-eosin staining method, magnification x 100.

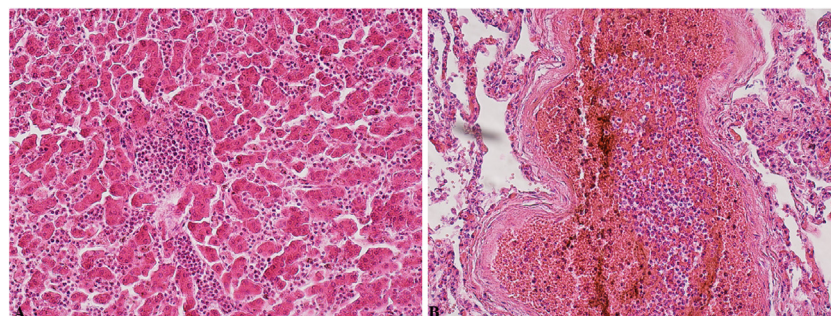


Fig. 4. Representative photomicrographs demonstrate: (A) extensive neutrophil infiltration in the liver tissue, magnification ×100; (B) extensive neutrophil infiltration in the pulmonary artery lumen, magnification x 200. The haematoxylin-eosin staining method.

in the intestinal flora, which represents a microbiome, can promote the translocation of pathogens into the blood stream and the development of nosocomial BSIs. The most common aetiology is the *Candida* species (47.3%), followed by enterobacteria (19.4%), mixed

infections, including *Klebsiella pneumoniae* (19.4%), and enterococci (13.9%) [6–10].

In the case presented here the administration of oral Vancomycin, which is highly active against the intestinal flora, could

have been responsible for the persistence and overgrowth of *Klebsiella pneumoniae* in the gastrointestinal tract.

4. Conclusions

We can assume that extremely high leucocytosis was a factor for unfavourable prognosis. The gut inflammatory injury caused by the severe CDI may be considered as the “second hit,” allowing the bacterial translocation and BSI. Careful consideration of antibacterial therapy and early symptom recognition may help prevent catastrophic events.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

The case report was approved by the Ethical Board of the Hospital of Traumatology and Orthopaedics, Riga, Latvia, Statement of 20 November 2020.

Consent

Informed consent could not be obtained as the patient died in the course of the disease.

Written informed consent was obtained from the Chief Physician of the Hospital of Traumatology and Orthopaedics for publication of this case report and accompanying images. A copy of the written consent may be provided to the Editor-in-Chief of this journal on request.

Author contribution

Dr. med. Iveta Golubovska conceptualization, project administration, writing the case report, literature analysis; Dr. Martins Malzubris operating surgeon-data collection; Dr. Luize Raga, operating surgeon – data collection; Dr. Dace Vigante – infectologist, data analysis, text corrections; Ass. Prof. Sergejs Isajevs – visual design and microphotography, Ass. Prof. Aleksejs Miscuks-discussion and project administration.

Iveta Golubovska, Aleksejs Miscuks: anaesthesiologists and intensive care specialists.

Martins Malzubris, Luize Raga: surgeons.

Dace Vigante: infectious diseases specialist.

Sergejs Isajevs: pathologist.

Registration of research studies

Not applicable.

Guarantor

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