Case Report

Methicillin-Resistant Staphylococcus aureus as a Probable Cause of Antibiotic-Associated Enterocolitis

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Antibiotic-associated diarrhea is typically associated with Clostridium difficile, particularly in the setting of antibiotic use [1]. However, prior to the identification of C. difficile and its toxins as contributors to healthcare-associated diarrhea in the mid-1970s, Staphylococcus aureus was recognized as a causative agent of antibiotic-associated enterocolitis (AAE). Staphylococcal enterocolitis was first described in the 1950s, but increasing prevalence of C. difficile in recent years has led to underrecognition of S. aureus as an etiology of nosocomial and antibiotic-associated diarrhea [1]. We present a case of enterocolitis and urinary tract infection caused by methicillin-resistant S. aureus following antibiotic treatment.

1. Introduction

The most commonly identified pathogen in healthcare-associated diarrhea is Clostridium difficile, particularly in the setting of antibiotic use [1]. However, prior to the identification of C. difficile and its toxins as contributors to healthcare-associated diarrhea in the mid-1970s, Staphylococcus aureus was recognized as a causative agent of antibiotic-associated enterocolitis (AAE). Staphylococcal enterocolitis was first described in the 1950s, but increasing prevalence of C. difficile in recent years has led to underrecognition of S. aureus as an etiology of nosocomial and antibiotic-associated diarrhea [1]. We present a case of enterocolitis and urinary tract infection caused by methicillin-resistant S. aureus (MRSA) following antibiotic treatment in a MRSA-colonized patient.

2. Case

An 87-year-old woman presented to the emergency department with three days of abdominal pain, nausea, vomiting, and copious diarrhea. She described watery stools occurring up to eight times each day, without blood or mucus. She reported fatigue and anorexia but denied fevers and chills, as well as dysuria or other urinary symptoms. Six days previously, she had been discharged after a week-long hospitalization for ST-elevation myocardial infarction, which included diagnostic cardiac catheterization via femoral access. During this hospitalization, she was also diagnosed with community-acquired pneumonia and was started on intravenous ceftriaxone and azithromycin, with transition to oral levofloxacin at discharge.

On initial examination, she was afebrile with heart rate of 91 and blood pressure 95/48 (slightly below her outpatient baseline). Oral mucosae were dry and abdomen was soft, nondistended and diffusely tender without peritoneal signs, suprapubic tenderness, or costovertebral angle tenderness. Initial labs revealed a neutrophil-predominant leukocytosis of 15,800 cells/μL; creatinine 1.31 mg/dL (previous baseline 0.65 mg/dL); and normal lactate, liver-associated enzymes, and lipase. Urinalysis demonstrated positive leukocyte esterase, 34 leukocytes/hpf, and negative nitrite. Fecal leukocytes and C. difficile PCR (Cepheid® Xpert® C. difficile) were negative. Abdominal plain films were unremarkable.

The patient was admitted for fluid resuscitation and symptomatic management with ondansetron and loperamide, with improvement of her abdominal pain and nausea. However, her profuse diarrhea persisted, and on hospital day 2, both urine and stool cultures obtained on admission grew MRSA. Abdominal CT revealed sigmoid...
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a causative agent of AAE is less established in recent Western

While MRSA is well-recognized as an important and serious

entD, seb

hla, hld, hlgA, hlgB, hlgC

Virulence genes

aur, cap8A, cap8B, cap8C, cap8D, cap8F, cap8G,
cap8L, cap8N, cap8M, cap8O, chp, geh, sbi, scn,
sspB, sspC

eyPS, fnb, sdrC

essA, essB, essC, essA, essB, essB

hysA, sak

icaA, icaB, icaR

isdA, isdB, isdD, isdF, isdG

MW0023

srtB

sspA

Staphylococcal enterotoxins (SE-B and D) which act as superantigens

Cytotoxins

Disruption of host complement activity, phagocytosis, and/or immune cell

chemotaxis

Host tissue adherence

Virulence proteins via unclear mechanisms, perhaps modulate host cell

apoptosis

Tissue degradation and invasion

Biofilm formation

Iron acquisition

Immune modulation

Modification of bacterial surface proteins

Modification of bacterial enzymes and cleavage of immunoglobulin G

bowel wall thickening consistent with colitis. The patient was

started on vancomycin via both intravenous (750 mg daily)

and oral (125 mg every 6 hours) routes with significant

improvement of her diarrhea the following day. Though

blood cultures remained negative, given her multifocal

esophageal echocardiography which showed no evidence of

endocarditis. She finished 10 days of oral and 14 days of

parenteral vancomycin and recovered completely.

Due to the overwhelming predominance of MRSA in the

stool culture and concomitant presence in the urine, isolates

from both sources underwent genotyping with whole-

genome sequencing. DNA was extracted and then se-

quenced using MiSeq Reagent Kit v3 (Illumina, San Diego,

CA, USA). Sequencing reads were assembled, and com-

parative genomic analyses were performed using Geneious

(Biomatters, Auckland, New Zealand) [2]. The isolates were

found to be genetically identical and shared several genes

potentially involved in pathogenesis (Table 1). Notably, the

staphylococcal enterotoxin B (seb) gene and precursor gene

for staphylococcal enterotoxin D (entD) were present.

3. Discussion

While MRSA is well-recognized as an important and serious

nosocomial and community-acquired pathogen, its role as

a causative agent of AAE is less established in recent Western

literature. AAE caused by enterotoxin-producing staphy-

lococci was initially described in the 1950s [3, 4]. However,
in 1978, Clostridium difficile and its toxins were identified as

the principle causative agents of post-antibiotic pseudo-

membranous colitis (S. aureus was also seen, though

accounted for a minority of cases) [5, 6]. Since that time,

authors have only rarely reported cases of MRSA AAE, with

more cases published in Japanese [7] compared to Western

literature [8]. However, a prospective study of stools neg-

ative for C. difficile toxin from patients with diarrhea found

MRSA in 13 out of 3210 stool specimens, with 11 isolates

producing staphylococcal enterotoxins [9]. Recently, Iwata

et al. conducted a comprehensive review of the literature

related to MRSA AAE and identified nine criteria that

support a causative relationship [10]. It is therefore possible

that MRSA constitutes an underappreciated cause of

AAE [11].

Similar to C. difficile infection, risk factors for develop-

ment of MRSA AAE include advanced age, immuno-

suppression, prolonged hospital stays, and previous

antibiotic treatment [12, 13]. For MRSA in particular, prior

fluoroquinolone use (as in our patient) is associated with an

increased risk [12]. Though MRSA AAE can have a very

similar clinical presentation to C. difficile, it is more likely to

involve the small intestine instead of cecum or colon, and

can result in localized bowel wall thickening on CT, as seen

in this case [9, 13, 14]. Diarrhea is typically profuse, large

volume, and watery, and patients with MRSA colitis are

more likely to have associated symptoms of nausea, vom-

iting, and fever [13].

Similar to the pathogenesis of C. difficile, MRSA en-

terocolitis is likely caused by a toxin-mediated mechanism.

More than 20 different staphylococcal enterotoxins (SEs)

have been identified [15]. Many have well-understood roles

in staphylococcal food poisoning, and several reports have

identified TSST-1 as well as SE-A, B, C, D, and E in cases of

S. aureus enterocolitis [7, 9, 10, 12]. Staphylococcal leuco-

cidin LukE-LukD also has proposed involvement in the

disease process via a cytotoxic mechanism, and in one case,

series was identified in 94% of MRSA enterocolitis isolates

[16]. The majority of MRSA are toxin-producing strains,

which may account for their relative prevalence (in com-

parison with MSSA) in cases of enterocolitis [15].

In cases of severe antibiotic-associated diarrhea when

C. difficile toxin testing is negative, stool culture should be

performed for further evaluation, and isolation of MRSA as

the predominant organism should suggest causation. Testing

for viral enteric pathogens (though not performed in this

case) is now more widely available, and these should also be

excluded. When MRSA is identified or suspected as the

Table 1: Putative and confirmed virulence and toxin genes and associated proteins detected in both MRSA isolates.

| Toxin genes | Clinically relevant downstream effects |
|-------------|--------------------------------------|
| entD, seb   | Staphylococcal enterotoxins (SE-B and D) which act as superantigens |
| hla, hld, hlgA, hlgB, hlgC | Cytotoxins |
| Virulence genes | Disruption of host complement activity, phagocytosis, and/or immune cell |
| | chemotaxis |
| | Host tissue adherence |
| | Virulence proteins via unclear mechanisms, perhaps modulate host cell |
| | apoptosis |
| | Tissue degradation and invasion |
| | Biofilm formation |
| | Iron acquisition |
| | Immune modulation |
| | Modification of bacterial surface proteins |
| | Modification of bacterial enzymes and cleavage of immunoglobulin G |

*Previously demonstrated in cases of MRSA antibiotic-associated enterocolitis.
cause of antibiotic-associated colitis, oral vancomycin is the recommended treatment [12]. While diarrheal symptoms often begin to resolve within 24 hours of initiation of vancomycin, typically a 10–14-day course of 125–250 mg daily is used to ensure adequate treatment, though data on exact dose and duration are sparse and warrant further study [12, 17]. Additionally, supportive care and symptomatic management are important, and as diarrhea tends to be very profuse, aggressive fluid resuscitation is often necessary.

Though C. difficile is the most common infectious cause of antibiotic-associated diarrhea, MRSA is a clinically relevant and likely underdiagnosed etiology. Our patient’s presentation with colitis following a recent course of antibiotics, negative C. difficile PCR, MRSA overgrowth on stool cultures to the exclusion of normal fecal flora, and rapid resolution of diarrhea following initiation of oral vancomycin was consistent with MRSA as the inciting pathogen.

Disclosure

The views expressed in this manuscript are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of the Army, Department of Defense, nor the U.S. Government.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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