Fatal infection with enterocolitis from methicillin-resistant \textit{Staphylococcus aureus} and the continued value of culture in the era of molecular diagnostics

Pooja Bhattacharyya\textsuperscript{a,b,1,2}, Andrew Bryan\textsuperscript{d,1,2}, Vidya Atluri\textsuperscript{c,2}, Jimmy Ma\textsuperscript{c,2}, Lindsey Durowoju\textsuperscript{d,2}, Anshu Bandhlish\textsuperscript{d,2}, Jim Boonyaratanakornkit\textsuperscript{a,c,*,2}.

\textsuperscript{a} Vaccine and Infectious Disease Division, Fred Hutch Cancer Research Center, Seattle, WA, 98109, USA
\textsuperscript{b} Division of Oncology, University of Washington, Seattle, WA, 98109, USA
\textsuperscript{c} Division of Allergy and Infectious Disease, University of Washington, Seattle, WA, 98195, USA
\textsuperscript{d} Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, 98195, USA

\textbf{A R T I C L E   I N F O}

\textbf{Keywords:}
Staphylococcus aureus
Enterocolitis
Immunocompromised
Stool cultures

\textbf{A B S T R A C T}

MRSA enterocolitis is under-recognized in the setting of PCR testing. In this case report, we describe risk factors, the importance of stool culture, and the third published case of MRSA enterocolitis in a patient with leukemia. In addition, we performed a retrospective analysis of all stool cultures at our institution that have grown \textit{Staphylococcus aureus}, and we describe an additional five cases. We also report the diagnostic yield of organisms detected by culture, but not on the FilmArray panel. While rare, these cases demonstrate that MRSA in stool may indicate a severe and potentially life-threatening infection, particularly in immunocompromised persons.

1. Introduction

Confirmed fatal infection with enterocolitis from methicillin-resistant \textit{Staphylococcus aureus} (MRSA) has rarely been reported in the US. The present case demonstrates the importance of recognizing MRSA as a potential pathogen in the setting of neutropenic enterocolitis during induction chemotherapy and the continued importance of stool culture in the era of molecular diagnostics.

2. Case report

A 72-year-old man with a history of clinically quiescent Crohn’s disease presented to the emergency department with fever, fatigue, altered mental status, and nausea/vomiting four days after a new diagnosis of acute myelogenous leukemia (AML) (Fig. 1A). He had tumor lysis syndrome with acute kidney injury (AKI) and hyperleukocytosis and required intensive care unit (ICU) admission. Given the initial diagnostic uncertainty regarding whether his multi-organ failure was related to tumor lysis or infection, he was also treated empirically with ceftazidime and vancomycin for possible septic shock. Antibiotic infusions were separated by over 12 h so that co-mixing was avoided [1]. Blood and urine cultures were sterile. Computed tomography (CT) of the chest, abdomen, and pelvis was unremarkable. He became neutropenic after cytodreductive therapy with hydroxyurea and cytarabine, and deferred sequelae after receiving dose-reduced G-CLAM (filgrastim, cladribine, cytarabine, and mitoxantrone). Cefazidime was continued for neutropenic prophylaxis, and vancomycin was stopped given the lack of evidence for active infection. Five days later, he again fevered. The following day, he reported mild abdominal pain and new diarrhea. In the setting of febrile neutropenia, an enteric pathogen panel was obtained. This panel consisted of a rapid PCR using the Biofire FilmArray GI panel for 13 bacteria, 4 parasites, and 5 viruses, plus a blood agar plate, primarily for the detection of \textit{Salmonella}, \textit{Campylobacter}, \textit{Shigella}, and \textit{Vibrio} species is performed if these organisms are detected on the PCR panel. No pathogens were detected by PCR, and loperamide was started. Two days later, the blood agar plate showed 4+ MRSA with reduced normal fecal flora (Fig. 1B and C). Due to his profound immunocompromised status,
oral vancomycin was started for possible MRSA enterocolitis. Gram-negative and anaerobic coverage was also broadened to piperacillin-tazobactam. The following day, he developed respiratory distress, was intubated, and had recurrence of AKI and shock. Vancomycin IV was added. CT of the abdomen and pelvis showed diffuse small bowel wall edema, thickening, dilatation measuring up to 6.2 cm, and bowel wall erythema and congestion, and Gram positive cocci (Fig. 1D). No surgical interventions were available, and the patient was transitioned to comfort care, expiring that same day. Postmortem evaluation revealed gross dilatation of the duodenum and jejunum with dusky discoloration, mucosal erythema and congestion, and Gram positive cocci (Fig. 1E). Focal mucosal erosions were noted in the stomach and cecum. No pseudomembranes were found. Cause of death was attributed to septic shock with multiorgan failure, secondary to MRSA enterocolitis.

3. Discussion

*Staphylococcus aureus* enterocolitis has been recognized as a cause of antibiotic associated colitis since the mid-20th century[2]. However, when attention shifted to *Clostridioides difficile* as the major infectious cause for antibiotic-associated diarrhea, reports of *Staphylococcus aureus* enterocolitis in English scientific literature declined, and awareness diminished. *Staphylococcus aureus* is now often disregarded when isolated from stool culture [3]. Most recent reports published on *Staphylococcus aureus* enterocolitis have been from Japan [2-4]. These and other reports identified gastric resection, older age, longer hospitalization, intestinal carriage, and prior antibiotic exposure as risk factors for *Staphylococcus aureus* enterocolitis [5-7].

| Antibiotic | MIC Value (mg/mL) | Interpretation |
|------------|------------------|----------------|
| Clindamycin | S <=0.5 | |
| Daptomycin | S <=0.5 | |
| Erythromycin | R >4 | |
| Levofloxacin | R >4 | |
| Moxifloxacin | R 4 | |
| Oxacillin | R >2 | |
| Tetracycline | S <=2 | |
| Trimethoprim - Sulfamethoxazole | S <=2 | |
| Vancomycin | S 1 | |

**Table 1**

| Organism group | N (%) | Comments |
|----------------|-------|----------|
| *Aeromonas* spp. | 30 (0.42%) | A. cariae (N = 7) |
| *Pseudomonas* spp. | 38 (0.53%) | A. hydrophila (N = 6) A. veronii (N = 10) Not determined (N = 5) |
| *Bacillus* spp. | 7 (0.10%) | |
| *Beta hemolytic streptococci* | 4 (0.06%) | |
| *Staphylococcus aureus* | 4 (0.06%) | |
| *Graminia holliae* | 1 (0.01%) | |
| *Fungi* | 112 (1.56%) | Aspergillus fumigatus (N = 2) Micrales (N = 3) Yeast (N = 107) |

* Percent is out of N = 7179 total enteric panels performed.

Patients with hematologic malignancies are also at risk for neutropenic enterocolitis and *Clostridioides difficile* infection (CDI) due to cytotoxic chemotherapy and antibiotic exposure, but reports of MRSA enterocolitis are rare [8,9]. Although targeted and less cytotoxic therapies against AML are being increasingly studied, intestinal complications, including neutropenic enterocolitis, remain problematic [10-13]. To our knowledge, there are only three cases of MRSA enterocolitis in the setting of acute leukemia reported in the literature. This is possibly due to underdiagnosis as stool cultures are not often obtained and now supplanted by PCR testing [14,15]. While our laboratory utilizes a blood...
In general, the gut microbiome can be an indicator of the presence of a pathogen. In this case, the presence of MRSA in the stool cultures likely indicated that MRSA was the cause of the enterocolitis.

MRSA enterocolitis can present with fever and vomiting, which can result in more profuse diarrhea and mucosal damage and dysbiosis, allowing for MRSA overgrowth and enterotoxin production. This, coupled with chemotherapy, neutropenia, and antibiotic exposure, may have predisposed to mucosal damage.

MRSA enterocolitis is likely a risk factor for invasive disease and sepsis. MRSA enterocolitis is a rare cause of neutropenic enterocolitis in patients with hematologic malignancies after induction chemotherapy and demonstrates the continued utility of stool culture in the era of molecular diagnostics.

Funding

This work was supported by the Fred Hutchinson Joel Meyer’s Endowment (J.B.), a new investigator award from the American Society for Transplantation and Cell Therapy (J.B.), and the Host Defense Training in Allergy and Infectious Diseases 5T32AI007044-45 (V.A.).

CRediT authorship contribution statement

Pooja Bhattacharyya: Data curation, Writing – original draft. Andrew Bryan: Data curation, Writing – original draft, Formal analysis. Vidya Atluri: Writing – original draft. Jimmy Ma: Writing – original draft. Lindsey Durowoju: Formal analysis. Anshu Bandlish: Formal analysis. Jim Boonyaratankornkit: Data curation, Writing – original draft.

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] K. Meyer, M. Santarossa, L.H. Danziger, E. Wenzler, Compatibility of ceftazidime-avibactam, ceftolozane-tazobactam, and piperacillin-tazobactam with vancomycin in dextrose 5% in water, Hosp. Pharm. 52 (3) (2017) 221–228.

[2] D.P. Kotler, E.M. Sordillo, A case of staphylococcus aureus enterocolitis: a rare entity, Gastroenterol. Hepatol. (N Y) 6 (2) (2010) 117–119.
[3] K. Iwata, A. Doi, T. Fukushima, G. Ohji, Y. Shirato, T. Sakai, H. Kagawa, A systematic review for pursuing the presence of antibiotic-associated enterocolitis caused by methicillin-resistant Staphylococcus aureus, BMC Infect. Dis. 14 (2014) 247.

[4] Z. Lin, D.P. Kotler, P.M. Schlievert, E.M. Sordillo, Staphylococcal enterocolitis: forgotten but not gone? Dis. Sci. 55 (2010) 1200–1207.

[5] J.M. Boyce, N.L. Havill, Noncommunal antibiotic-associated diarrhea associated with enterotoxin-producing strains of methicillin-resistant Staphylococcus aureus, Am. J. Gastroenterol. 100 (8) (2005) 1828–1834.

[6] Y. Ogawa, T. Saraya, T. Koide, K. Kikuchi, K. Ohkuma, K. Araki, H. Makino, S. Yonetani, H. Takizawa, H. Goto, Methicillin-resistant Staphylococcus aureus enterocolitis sequentially complicated with septic arthritis: a case report and review of the literature, BMC Res. Notes 7 (2014) 21.

[7] D.S. Acton, M.J. Plat-Sinnige, W. van Wamel, N. de Groot, A. van Belkum, Intestinal carriage of Staphylococcus aureus: how does its frequency compare with that of nasal carriage and what is its clinical impact? Eur. J. Clin. Microbiol. Infect. Dis. 28 (2) (2009) 115–127.

[8] A. Chubachi, S. Nishimura, Y. Endo, A.B. Miura, Methicillin-resistant staphylococcal enterocolitis developed after induction chemotherapy in a case of acute promyelocytic leukemia, Rinsho Ketsueki 30 (8) (1989) 1319–1320.

[9] A. Rothman, J. Lio, Y. Lee, M.R.S.A. Colitis, An under-recognized cause of septic shock, Abstr. Am. Thoracic Soc. (2020). May 22.

[10] N.J. Short, M. Konopleva, T.M. Kadia, G. Borthakur, F. Ravandi, C.D. DiNardo, N. Daver, Advances in the treatment of acute myeloid leukemia: new drugs and new challenges, Cancer Discov. 10 (4) (2020) 506–525.

[11] R. Xia, X. Zhang, Neutropenic enterocolitis: a clinico-pathological review, World J. Gastrointest. Pathophysiol. 10 (3) (2019) 36–41.

[12] M. Gorschulter, U. Mey, J. Strehl, V. Schmitz, C. Rabe, K. Pauls, C. Zöike, I. Schmidt-Wolf, A. Glasmacher, Invasive fungal infections in neutropenic enterocolitis: a systematic analysis of pathogens, incidence, treatment and mortality in adult patients, BMC Infect. Dis. 6 (2006) 35.

[13] M. Ueda, N. El-Jardii, B. Cooper, P. Caimi, L. Baer, M. Kolb, L. Brister, D.N. Wald, F. Otegbeye, H.M. Lazarus, B.M. Sandmaier, B. William, Y. Sauntharajah, P. Woott, J.W. Jacobberger, M. de Lima, Low-dose azacitidine with DNMT1 level monitoring to treat post-transplantation acute myelogenous leukemia or myelodysplastic syndrome relapse, Biol. Blood Marrow Transpl. 25 (6) (2019) 1122–1127.

[14] D.L. Siegel, P.H. Edelstein, I. Nachamkin, Inappropriate testing for diarrheal diseases in the hospital, JAMA 263 (7) (1990) 979–982.

[15] S.G. Beal, E.E. Tremblay, S. Toffel, L. Velez, K.H. Rand, A Gastrointestinal PCR panel improves clinical management and lowers health care costs, J. Clin. Microbiol. 56 (1) (2018).

[16] A.E. Kates, D. Thapaliya, T.C. Smith, M.L. Chorazy, Prevalence and molecular characterization of Staphylococcus aureus from human stool samples, Antimicrob Resist Infect Control 7 (2018) 42.

[17] G. De Hertogh, K. Geboes, Crohn’s disease and infections: a complex relationship, Med. Gen. Med. 6 (3) (2004) 14.

[18] T. Hueso, K. Elpe, C. Mayeur, A. Gatse, M. Joncquel-Chevallier Curt, G. Gricourt, C. Rodriguez, C. Burdet, G. Ulmann, C. Neut, S.E. Amini, P. Lepage, B. Raymond, C. Willekens, J.B. Michel, S. De Botton, I. Yakoub-Agha, F. Gottrand, J.L. Deseyn, M. Thomas, P.L. Woerther, D. Seguy, Impact and consequences of intensive chemotherapy on intestinal barrier and microbiota in acute myeloid leukemia: the role of mucosal strengthening, Gut. Microbes. 12 (1) (2020), 1800897.

[19] A. Rashidi, Z. Zhu, T. Kaiser, D.A. Manias, S.G. Holtan, T.U. Rehman, D. J. Weisdorf, A. Khoruts, G.M. Dunny, C. Staley, Vancomycin-resistance gene cluster, vanS, in the gut microbiome of acute leukemia patients undergoing intensive chemotherapy, PLoS ONE 14 (10) (2019), e0223990.

[20] A.B. Lane, N.K. Copeland, F. Ommus-Leone, J.V. Lawler, Methicillin-resistant staphylococcus aureus as a probable cause of antibiotic-associated enterocolitis, Case Rep. Infect. Dis. 2018 (2018), 3106305.

[21] J.R. Galloway-Pena, Y. Shi, C.B. Peterson, P. Sahasrabhojane, V. Gopalakrishnan, C.E. Brumlow, N.G. Daver, M. Alfayez, P.C. Boddu, M.A.W. Khan, J.A. Wargo, K. A. Do, R.R. Jeng, D.P. Kontoyiannis, S.A. Sheline, Gut microbiome signatures are predictive of infectious risk following induction therapy for acute myeloid leukemia, Clin. Infect. Dis. 71 (1) (2020) 63–71.

[22] M. Bergevin, A. Marion, D. Farber, G.R. Golding, S. Levesque, Severe MRSA enterocolitis caused by a strain harboring enterotoxins D, G, and I, Emerg. Infect. Dis. 23 (5) (2017) 865–867.