Bullous cellulitis as an extraordinary manifestation of a *Vibrio cholerae* O1 Ogawa infection

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**ABSTRACT**

*Vibrio cholerae* is a gram-negative bacterium synonymous with its namesake disease, cholera. Thus, gastrointestinal symptoms are the norm and *V. cholerae* is very rarely associated with skin and soft tissue infections. We describe a case of a 63-year-old Chinese woman with multiple medical comorbidities on corticosteroid therapy who developed fever and a painful swelling on her left leg after being pricked by a branch while gardening. There was no abdominal pain, vomiting or diarrhea. A diagnosis of bullous cellulitis was made clinically, and blood was sent for bacteriological culture. A beta-hemolytic comma-shaped gram-negative bacillus was isolated from the blood. It was also oxidase-positive and produced an acid/alkaline (A/K) reaction on triple sugar iron agar. It was identified biochemically as *Vibrio cholerae*. After additional testing, it was found to be of the O1 serogroup and Ogawa serotype. The infection resolved following a 10-day course of high-dose co-trimoxazole therapy.

**Keywords:** *Vibrio cholerae* O1; Ogawa; bullous cellulitis; co-trimoxazole.

**INTRODUCTION**

*Vibrio cholerae* is a facultative human pathogen that resides in various aquatic environments (Reidl & Klose, 2002). Accordingly, infections with *V. cholerae* typically ensue following the ingestion of tainted seafood or sewage-contaminated food and water. Patients customarily present with gastrointestinal symptoms such as profuse watery diarrhea and vomiting (i.e., the characteristic symptoms of cholera) – extraintestinal manifestations are few and far between. Extraintestinal *Vibrio* skin and soft tissue infections (SSTI) may take the form of bullous skin lesions, localised cellulitis or even necrotizing soft-tissue infections with secondary septicemia (Oliver, 2005). In *Vibrio*-related SSTIs, *Vibrio vulnificus*, *Vibrio parahaemolyticus* and *Vibrio alginolyticus* are the ‘usual suspects’ rather than *V. cholerae* (Aguinaga et al., 2009). Although non-O1 *V. cholera* has been previously reported to cause SSTIs, there is a paucity of reports specifically implicating *V. cholerae* O1 in such infections (Issack et al., 2008; Aguinaga et al., 2009). To the best of our knowledge, this is the first report of bullous cellulitis attributable to *V. cholerae* O1 Ogawa from Malaysia.

**CASE REPORT**

A 63-year-old Chinese housewife with thalassemia trait, systemic lupus erythematosus (SLE) on prednisolone for the past 20 years, and chronic hepatitis B on tenofovir for the past 9 years presented to UKM Medical Centre with an acute onset of severe left leg pain and swelling, impairing her ability to ambulate. She was gardening a day before the onset of her symptoms, during which a sharp branch pierced the skin of her shin. Although she applied an antiseptic solution on the wound, the affected leg became progressively swollen and painful overnight. By the next morning, the wound became erythematous and she developed fever with chills and rigors. There was no associated abdominal pain, vomiting or diarrhea. She denied a recent history of travel. Similarly, there was also no recent history of eating seafood or any hawker/stall food. No other family members were having similar symptoms.

On arrival at our emergency department, she was alert and conscious. Her blood pressure was 111/55 mmHg, pulse rate was 98 beats per minute and body temperature was 37.8°C. Examination of the left leg revealed a visible swelling from below the knee until the ankle, with a small wound on the shin measuring 1 × 2 cm which was producing a serous discharge. Multiple bullae were also seen, and the left leg was erythematous, warm and tender. Pitting edema was detected until the mid-shin level. Initial blood investigations revealed an elevated total white cell count of 24 × 10⁹/L (with a predominance of neutrophils), a low hemoglobin level of 7.9 g/dL, a normal platelet count of 276 × 10⁹/L and a raised C-reactive protein level of 20 mg/dL. Her initial diagnosis was left leg cellulitis.

A culture of the wound swab taken during admission was heavily mixed and thus of limited clinical value. A blood sample was sent for bacteriological culture and IV ampicillin-sulbactam 1.5 g thrice daily was commenced empirically. The following day, she was referred to the orthopedic team to rule out left leg necrotizing fasciitis, in view of the worsening cellulitis. A wound debridement was undertaken, following which her diagnosis was revised to left leg bullous cellulitis.
By the second day of admission, comma-shaped gram-negative bacilli were cultured from the blood (Figure 1). The bacteria grew as non-lactose fermenters on McConkey agar, formed beta-hemolytic colonies on blood agar (Figure 2) and were oxidase-positive. Triple sugar iron (TSI) agar inoculation revealed an acidic butt and an alkaline slant with no gas formation. Based on the TSI reaction, we utilized a biochemical identification kit for Enterobacteriaceae and other non-fastidious gram-negative rods known commercially as API 20 E (bioMérieux, France) and identified the organism as *Vibrio cholerae* (profile no.: 5347125) with an excellent discrimination of 99.3%. Notwithstanding this ‘smoking gun’ evidence, owing to the peculiarities of the case, we still attempted the hanging drop test (which revealed darting motility) and sub-cultured the isolate on thiosulfate-citrate-bile salts-sucrose (TCBS) agar (which yielded yellow colonies with a flat surface, as shown in Figure 3). Her stools were also cultured to determine if she was excreting the pathogen through her stools, and as expected, it was negative for enteric pathogens (including *V. cholerae*).

Following supplementary tests by the National Public Health Laboratory in Sungai Buloh, our isolate was formally identified as *Vibrio cholerae* O1 Ogawa. Antibiotic susceptibility testing (AST) via the disk diffusion method revealed the organism to be resistant to ampicillin but susceptible to co-trimoxazole, tetracycline and chloramphenicol. We did not test against ampicillin-sulbactam because our AST guideline (i.e. the Clinical and Laboratory Standards Institute document M45) only published ampicillin-sulbactam breakpoints for *Vibrio* species other than *V. cholerae*. Based on this, the patient’s antibiotic therapy was switched to four tablets of oral cotrimoxazole twice daily, with each tablet containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole. Her leg wound was also dressed and reviewed daily by the orthopedic team. She completed 10 days of oral cotrimoxazole in the ward and remained afebrile. A repeat blood culture at this juncture yielded no growth, as well as all the intraoperative pus and tissue cultures. By now, her C-reactive protein level had decreased to 0.57 mg/dL. She was discharged home with an instruction to continue taking oral co-trimoxazole for another four days.

**DISCUSSION**

*V. cholerae* is conventionally classified based on its somatic or ‘O’ antigen (which is part of the bacterium’s outer membrane lipopolysaccharide) which dictates its serogroup, its biotype (i.e., classical or El Tor) and its serotype (i.e., Ogawa, Inaba or Hikojima) (Kaper et al., 1995). Thus, any *V. cholerae* with somatic antigen type-1 like ours is of the O1 serogroup and may be designated as *V. cholerae* O1. While in excess of 200 ‘O’ serogroups are recognized, only serogroups O1 and O139 have been linked to severe disease and pandemics of cholera (Reidl & Klose, 2002). It has been reported the El Tor biotype has since replaced the classical biotype to become the globally dominant biotype following the seventh cholera pandemic in 1961 (Pradhan et al., 2010). The presence of hemolysis in our blood agar suggests that our isolate was of the El Tor biotype, because strains of the classical biotype do not secrete hemolysins (Singh et al., 2001). Biotyping can also be accomplished by carrying out cholera toxin B subunit gene (*ctxB*) sequencing or bacteriophage-mediated lysis (Son et al., 2011). Although *V. cholerae* O1 has three serotypes (Ogawa, Inaba and Hikojima) studies have shown that the bacterium can undergo serotype interconversions in response to stressors, with serotype Hikojima being the least stable of the three (Alam et al., 2016). Where disease severity is concerned, both
Ogawa and Inaba serotypes cause severe cholera (Khan et al., 2010). Serotype switching is plausibly a bacterial mechanism to evade host immunity in an individual who had been previously infected with a certain serotype. Accordingly, the fact that our isolate was of the Ogawa serotype is probably only of academic interest.

The gastrointestinal symptoms of V. cholerae O1 are orchestrated principally by cholera toxin (CT), following the ingestion of the pathogen and its colonization of the human gut. Despite this, non-toxigenic strains of V. cholerae O1 exist in the environment, and in fact, the majority of environmental strains do not secrete CT (Singh et al., 2001). Thus, it is likely that our patient did not suffer from the classical cholera symptoms because the strain that infected her did not secrete CT. Also, due to the nature of her presenting symptoms, it is highly probable that the organism was transmitted not via ingestion of contaminated food, but through traumatic inoculation by a tree branch while gardening. The branch could have been in contact with soil contaminated with V. cholerae. Such contamination can occur if the soil is exposed to human feces, as was the case of a cholera outbreak that occurred in a tea plantation in Assam, India (Mahanta et al., 2013). The multiple medical comorbidities (particularly SLE) suffered by our patient and her corticosteroid therapy could have resulted in an immunosuppressed state which only heightened her risk for SSTI. Environmental strains of V. cholerae O1 have been found to secrete a cytotoxic hemolysin designated as VcVac (Coelho et al., 2000). Since our isolate was evidently beta-hemolytic when cultured on blood agar, we postulate that this hemolysin (or an analogous cytotoxin) played an integral role in the disease pathogenesis, akin to how Streptococcus pyogenes (a notorious beta-hemolytic bacterium) causes cellulitis.

Like most clinically significant bacteria, V. cholerae is not spared from antibiotic resistance issues. Globally, the resistance rate of environmental V. cholerae O1/O139 isolates is 59% to cotrimoxazole, 28% to erythromycin, 14% to tetracycline and 5% to doxycycline (Yuan et al., 2022). Thus, all clinical microbiology laboratories, including those in developing countries, should perform AST for every V. cholerae isolate because its antibiogram is imperative for optimal patient management. AST for V. cholerae can be achieved through the comparatively low-cost disk-diffusion method which provides inhibitory zone diameter measurements – this obviates the need to obtain minimal inhibitory concentration values which are more costly (CLSI, 2015). Our isolate was resistant to ampicillin but susceptible to tetracycline and co-trimoxazole (which are commonly available and relatively narrow-spectrum antibiotics). Although tetracyclines (i.e., tetracycline and doxycycline) are widely regarded as the first-line antibiotics for cholera, we opted for co-trimoxazole instead because our patient had an SSTI rather than cholera. Not only is co-trimoxazole bactericidal (while tetracyclines are bacteriostatic), it also penetrates well into skin and soft tissues (Stevens et al., 2014). Unlike in the case of melioidosis, combination antibiotic therapy is not routinely practiced for V. cholerae infections (Ding et al., 2013). Our patient was successfully managed with co-trimoxazole monotherapy as evidenced by a negative blood culture after 10 days of therapy.

CONCLUSION

In conclusion, although very infrequently encountered, bullous cellulitis (or other SSTIs) can be caused by V. cholerae O1. The archetypal gastrointestinal symptoms of acute cholera need not be mandatorily present in such cases. The onus is therefore on the laboratory to have a high index of suspicion when faced with a gram-negative bacillus that has a comma-shaped morphology and is oxidase-positive despite exhibiting an acid/alkaline TSI reaction. Conclusive identification can be easily accomplished through commercially available biochemical test kits for gram-negative bacilli. Although we recommend co-trimoxazole for treatment, due to the probability of drug-resistance, the need to perform AST prior to definitive therapy cannot be overemphasized.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

REFERENCES


