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CASE REPORT

Nonpigmented *Chromobacterium violaceum* bacteremic cellulitis after fish bite

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KEYWORDS

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A case of nonpigmented *Chromobacterium violaceum* bacteremic cellulitis after fish bite in Taiwan is reported. The patient was successfully treated with ciprofloxacin and doxycycline for an extended period. *Chromobacterium violaceum* should be listed in the differential diagnosis of patients with nonspecific cellulitis associated with marked leukocytosis and rapid progression to septicemia either with or without a distinct history of exposure to water or soil. A combination of prompt diagnosis, optimal antimicrobial therapy, and adequate therapeutic duration for *C violaceum* infection is the key for successful therapy.

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Introduction

Chromobacterium violaceum is known to be a natural inhabitant with ubiquitous distribution in soil and water of tropical and subtropical areas.¹ Human infections are rare and sporadic in the world. Nevertheless, its excessive virulence usually causes life-threatening sepsis once contracted.^{1–3} Infection caused by the nonpigmented strain of *C violaceum* is rare, but it does cause the same serious morbidity as the pigmented strain does.² Clinically, it is impossible to differentiate between infections caused by

C violaceum and other possible microorganisms by patient's initial presentation. It is, therefore, important to alert the clinician to be aware of this pathogen and its clinical spectrum of infection. Here, a case with nonpigmented *C violaceum* bacteremic cellulitis after fish bite in Taiwan is reported. He was successfully treated with ciprofloxacin and doxycycline for an extended period. A combination of prompt diagnosis, optimal antimicrobial therapy, and adequate therapeutic duration for *C violaceum* infection is the key for successful therapy.

Case report

In August 2009, a 64-year-old diabetic married man was brought to the emergency room of Buddhist Tzu Chi General Hospital, Taipei Branch, located in Taipei County, with a 3-

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day history of intractable pain over right lower extremity, severe headache, and persistent high fever. Three days before this entry, he had experienced a fish bite during fishing along a river. This fish (*Tilapia*) slipped and fell on his right foot when it was just removed from the hook and then it bit him. He stated that he did not wade in water before and after the injury. Progressive swelling, redness, and pain over his right foot developed in the subsequent days. His medical histories were significant for diabetic mellitus, ureteral stone, and hepatitis B carrier. At emergency room, he presented as conscious with toxic appearance and marked prostration. His blood pressure was 146/94 mmHg, body temperature was 38.1°C, the respiratory rate was 20 breaths/min, and the heart rate was 114 beats/min. Significant laboratory investigations revealed the following: total white blood cell count, 38,500/ μ L with a left shift; hemoglobin, 15.6 g/dL; platelet count, 245×10^3 / μ L; C-reactive protein, 27.51 mg/dL (nephelometry; reference range, <0.5 mg/dL); blood glucose, 787 mg/dL (reference range, 70–115 mg/dL); serum creatinine, 1.46 mg/dL (reference range, 0.7–1.2 mg/dL); lactate dehydrogenase, 235 IU/L (reference range, 133–225 IU/L); sodium, 124 mmol/L (reference range, 136–145 mmol/L); and normal serum lactate and osmolality. A chest radiograph and abdominal ultrasound revealed no significant abnormality.

On admission, the patient was febrile, with a body temperature of 39°C. His vital signs included a heart rate of 120 beats/min, a respiratory rate of 24 breaths/min, and a blood pressure of 110/70 mmHg. The lesion around the fish bite location healed well. Erythematous change with local heat and profound tenderness, but no palpable crepitation, and two vesicles on the right foot were found (Fig. 1). Treatment was initiated with parenteral amoxicillin/clavulanate plus gentamicin and doxycycline. On Day 2, fever persisted, and pain over his right foot exacerbated. The follow-up C-reactive protein content was 39.9 mg/dL. A random cortisol level was 3.31 μ L, which was suggestive of sepsis-related adrenal insufficiency. The value of D-dimer was 922.44 ng/mL (reference range, <500 ng/mL); fibrinogen was 606.1 mg/dL (reference range, 200–400 mg/dL); and glycated hemoglobin (HbA1C) was 10.5% (reference



Figure 1. Erythematous change with two vesicles over right foot.

range, 4–6%). Amoxicillin/clavulanate was replaced by ceftriaxone because of the positive report of Gram-negative bacilli in blood cultures. Needle aspiration was performed from the bullas. About 1 mL of clear yellowish fluid was drained out for studies. The Gram stain gave a negative result. *Chromobacterium violaceum* was subsequently isolated from the two sets of blood cultures. Identification was confirmed by VITEK 2 System (bioMérieux) and API-20 NE substrate-utilization test panel kit, Phoenix 100 System (Beckson Diagnostic Instrument System). This bacterium is beta-hemolytic and has positive catalase and oxidase reactions. They were round and slightly raised with light blue color, not purple, on blood agar plate (Fig. 2). The colonies were not pigmented even after a 10-day period of incubation. Antibiotic susceptibility tests revealed susceptibility to ciprofloxacin, piperacillin–tazobactam, levofloxacin, meropenem, aztreonam, ceftazidime, and cefepime; intermediate susceptibility to gentamicin and amikacin; and resistance to ampicillin–sulbactam. In this regard, the antimicrobial therapy was tailored to parenteral ciprofloxacin plus doxycycline. In addition, prednisolone (1 mg/kg everyday) for his relative adrenal insufficiency was initiated on Day 3. Repeated blood culture obtained 1 week after hospitalization yielded no microorganism. The studies for leptospirosis and rickettsial infection were negative. He was discharged without sequelae after treatment for 18 days. Therapeutic regimen with oral ciprofloxacin 500 mg every 12 hours was maintained for 2 months in outpatient follow-up. There was no evidence of recurrence after 3 months of evaluation.

Discussion

This case illustrates the importance of early appropriate antimicrobial therapy to patient with *C. violaceum* infection

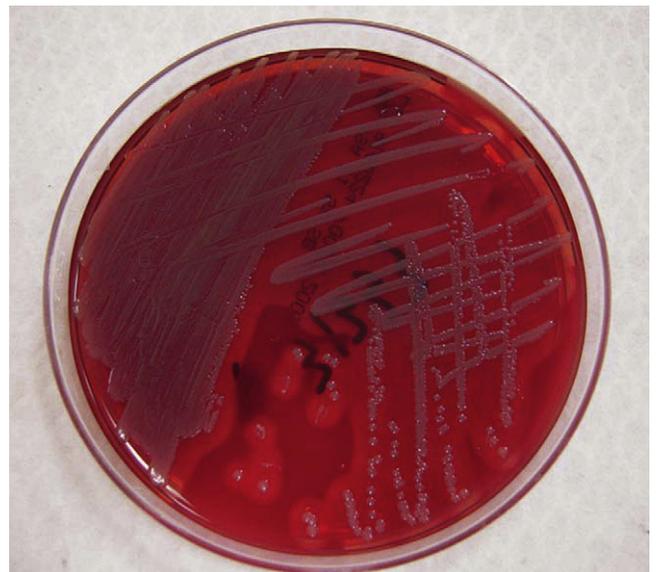


Figure 2. The colonies were revealed to be round and slightly raised with light blue in color, not purple, on blood agar plate. They were not pigmented even after a 10-day period of incubation.

after fish bite with subsequent local infection in progression. It is impossible to differentiate between the infections caused by *C. violaceum* and other possible microorganisms, including *Staphylococcus* spp., *Streptococcus* spp., *Aeromonas* spp., *Vibrio* spp., *Leptospira* spp., and *Burkholderia pseudomallei*, by patient's initial presentation. Therefore, the initial choice of antimicrobial therapy for such infection should be broad enough to cover all of the possible microorganisms. Otherwise, the patient's outcome will not be satisfied. To date, only six cases with *C. violaceum* infection have been reported in Taiwan. Clinical features of these patients and this reported case are listed in Table 1.^{4–8} In view of the data, the case fatality rate was 65% (four of seven), consistent with the report in the literature.¹ Clinical spectrum of *C. violaceum* infection has a wide range, including septicemia; cellulitis; lymphadenitis; pneumonia; visceral abscesses involving the liver, spleen, brain, and lung; urinary tract infection; gastroenteritis; intra-abdominal abscess; conjunctivitis; nasopharyngeal abscess; septic spondylitis; osteomyelitis; brain abscess; and meningitis.^{1–3,9} This patient represented a rapidly progressive cellulitis with sepsis. As shown in Table 1, six patients (85%) had the problem of broken skin lesion and subsequently progressed to cellulitis, consistent with literature review results.^{1–3,8} Nevertheless, it is still possible to get this infection from oral route or after near drowning.¹⁰ Furthermore, multiple abscesses could be the patient's initial manifestation.¹¹

Although *C. violaceum* is a normal habitant and is ubiquitous in soil and water, the infected cases were few and sporadic in the world.^{1–3} It may indicate the low infectivity of *C. violaceum*. However, Miller et al.¹² had conducted a study in 1988 comparing the virulent and avirulent strains of *C. violaceum*, in which virulent strain had elevated levels of superoxide dismutase and catalase that may protect this microorganism from phagocytic attack in humans. Thus, it is possible that whether patients developed this infection may depend on the strain of *C. violaceum* they contracted. However, its excessive virulence usually causes life-threatening sepsis once contracted.^{1–3} In this study, all of the patients were bacteremic with obvious leukocytosis in their initial presentations, consistent with the virulent characteristic of this bacterium. There were pigmented and nonpigmented colonies, with pigmented strains predominating.^{1–3} Violacein, an antioxidant, from the pigmented strain has a purple pigment giving it its typical color. Interestingly, violacein has been considered to be a natural antibiotic, and the biosynthesis, biological activities, and the diverse effects of this pigment have been well studied. As we know, aztreonam, a monocyclic beta-lactam antibiotic (a monobactam), is originally isolated from *C. violaceum*.¹³ In addition, this bacterium produces many antibiotics used clinically and industrially.¹⁴ The colonies cultured from this reported case were nonpigmented, which had not been reported in Taiwan previously. The nonpigmented strain of *C. violaceum* seems to be as virulent as the pigmented strain.³

Whether innate immunologic dysfunction plays an important role in *C. violaceum* infection or not is still controversial.^{1,3} Although chronic granulomatous disease had been considered the risk factor since the report from Macher et al. in 1982,¹⁵ most of the cases reported in the

literature were healthy. Of the cases in Taiwan, only this reported case was immunocompromised. Probably, the uncontrolled diabetes predisposed him to this infection during the accident. There were only three patients (42.9%) with the obvious history of exposure to water or soil, which was inconsistent with literature. Accordingly, exposure to water or soil or no exposure is not the crucial point in consideration of *C. violaceum* infection. However, with the increasing outdoor activity, people may be at a greater risk of *C. violaceum* infection. Isolation of *C. violaceum* by culture from a clinical specimen (blood, abscess fluid, or skin exudates) is the gold standard of diagnosis. There is no diagnostic serologic test.

Optimal antimicrobial treatment and duration of *C. violaceum* infection are unknown. It is usually susceptible to fluoroquinolones, chloramphenicol, tetracycline, trimethoprim–sulfamethoxazole, imipenem, and gentamicin.^{1–3} According to the literature review, *C. violaceum* is frequently intrinsically resistant to penicillins and cephalosporins.^{16–18} Increased β -lactamase activity in *C. violaceum* has been reported in a study by Farrar et al. in 1976.¹⁹ In 1988, Aldridge et al.¹⁷ had conducted a study for the comparison of the *in vitro* activities of ciprofloxacin and other antimicrobial agents against clinical strains of *C. violaceum*, in which ciprofloxacin was found to be the most active drug. In this study, the resistance rates of drugs to various cephalosporins are shown as follows: cephalothin (100%), cefamandole (100%), cefoxitin (36%), ceftizoxime (64%), ceftriaxone (36%), and cefotaxime (45%). This result indicates that the group of cephalosporins did not exhibit a reliable susceptibility test to *C. violaceum*, therefore, is not the drug of choice for this infection. On the other hand, cefazolin, oxacillin, amoxicillin/clavulanate, or ampicillin/sulbactam, which used to be the first-line antibiotics for common skin and soft tissue infections, are ineffective to unusual pathogens, including *Vibrio* spp., *Aeromonas* spp., *Leptospira* spp., *Burkholderia pseudomallei*, and also *C. violaceum*, which are endemic in Taiwan. Initial antimicrobial therapy with this first-line antibiotic alone for the relevant infection is, therefore, not optimal. In this reported patient, the initial antimicrobial coverage consisted of parenteral amoxicillin/clavulanate and gentamicin, and oral doxycycline. He seemed to respond very well to it. Thus, this combination therapy could be an initial option in treating patients with skin and soft tissue infection caused by relevant pathogens in Taiwan. Subsequently, definite therapy, of course, should be tailored promptly to drug susceptibility test. To give targeted therapy for *C. violaceum* infection, a fluoroquinolone in combination with one of the aminoglycosides represents the best treatment regimen according to *in vitro* data and clinical experience in literature.^{9,17} However, it is worth noting that several patients had experienced relapse or recurrence even after completion of therapy with clinical cure for *C. violaceum* infection.^{18,20,21} The pathogenesis for the frequent relapse or recurrence in patients with *C. violaceum* infection is still unknown. It is possible that occult microabscess or hidden septic focus may persist in the patient's internal organs despite adequate treatment. Therefore, treatment with parenteral antimicrobial agent was recommended for 2–4 weeks and was to be maintained with oral agents (e.g. trimethoprim–sulfamethoxazole,

Table 1 Clinical features of seven cases with *Chromobacterium violaceum* infection in Taiwan

Case	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Present case
Year	1968	1998	1998	2002	2003	2005	2009
Age (years)/sex	2/F	44/M	73/F	5/M	20/M	80/F	64/M
Clinical presentation	Cellulitis	Cellulitis	Cellulitis Septic spondylitis	Cellulitis Conjunctivitis Nasopharyngeal abscess	Intra-abdominal abscess	Cellulitis	Cellulitis
Comorbidity	No	Gall bladder stones after laparoscopic cholecystectomy	No	No	No	No	Diabetes Adrenal insufficiency
Exposure to contaminated water/soil	Yes	No	No	No	No	Yes	Yes
Blood culture	+	+	+	+	+	+	+
Antibiotic use (initial drug)	Chlorophenicol + gentamicin	Piperacillin (oxacillin)	Ciprofloxacin + piperacillin (cefazolin)	Penicillin + oxacillin + netilmicin (cefazolin)	Flomoxef	Levofloxacin (cefotaxime)	Ciprofloxacin (augmentin + gentamicin) Doxymycin
Initial white blood cell count (mm ³)	20,800	19,500	11,000	21,750	21,000	16,860	38,500
Outcome	Died	Died	Survived	Died	Died	Survived	Survived
Reference	Wu et al. ⁴	Chou et al. ⁵	Chou et al. ⁵	Shao et al. ⁶	Chen et al. ⁷	Change et al. ⁸	

F = female; M = male; + = positive.

doxycycline, or fluoroquinolones) for an extended period (2–3 months) to prevent relapse in patients with *C violaceum* infection.^{9,17,22}

In conclusion, patients with a distinct history of traumatic injury by creatures in river with subsequent local infection in progression should alert the clinician to list *C violaceum* as the probable pathogen. A combination of prompt diagnosis, optimal antimicrobial therapy, and adequate therapeutic duration for *C violaceum* infection is the key for successful therapy.

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