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Osteomyelitis Caused by *Enterobacter cancerogenus* Infection following a Traumatic Injury: Case Report and Review of the Literature

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We report a case of osteomyelitis caused by *Enterobacter cancerogenus* resistant to aminopenicillins in a 56-year-old male who had a motorcycle accident and suffered from multiple bone fractures with abundant environmental exposure. *E. cancerogenus* has rarely been associated with human infections, and its clinical significance remains unclear.

CASE REPORT

A previously healthy 56-year-old lawyer had a severe motorcycle accident, in which he was thrown onto the ground. He suffered from an open fracture of the proximal third of the right leg, a right acromioclavicular (AC) luxation and multiple fractures in other body parts.

He immediately underwent surgery with reduction and external fixation of the open tibial fracture. A single dose of cefamandole (2 g) given intravenously (i.v.) was administered as prophylaxis at the time of anesthesia. Empirical therapy with amoxicillin-clavulanic acid (2.2 g given i.v. every 8 h) and metronidazole (500 mg given i.v. every 8 h) was introduced, starting from the day following the intervention. A week later, another surgery was performed in order to reduce the AC luxation and to insert an external fixator on the right ulna. Metronidazole therapy was stopped after 2 weeks.

Four weeks after admission, while on continued antibiotic treatment with amoxicillin-clavulanic acid, the patient started complaining of increasing leg pain, with concomitant appearance of spontaneous purulent drainage from the wound on the anterior tibial side. The patient remained apyretic with normal white blood cells, an erythrocyte sedimentation rate of 38 mm/h, C-reactive protein level of 8.2 mg/liter (normal values, 0 to 5 mg/liter), and fibrinogen level of 445 mg/dl. An X-ray of the right leg showed that the fracture had not healed.

A swab culture of the purulent wound grew *Enterobacter cancerogenus* resistant to aminopenicillins (in the presence or absence of β-lactamase inhibitor) and to cefazoline: amoxicillin-clavulanic acid was therefore stopped, and a new antibiotic regimen consisting of levofloxacin (500 mg given i.v. once a day) plus ceftriaxone (2 g given i.v. once a day) was chosen on the basis of the susceptibility tests.

At the end of the fifth week, the patient underwent extensive debridement with resection of infected and necrotic-appearing areas of the tibial bone. An Ilizarov ring fixator was positioned. *E. cancerogenus* was cultured again from the bone specimens collected during the operation. The resistance pattern was unchanged from that of the previous isolate, and no change in antibiotic treatment was required. In the following days, the rapid recovery of the lesion allowed the uneventful application of a skin graft. An X-ray showed an overt tendency toward healing, with newly formed bone tissue seen at the site of fracture. Inflammatory markers returned to values in the normal range.

The patient was discharged after 7 weeks of i.v. treatment with levoxacin and ceftriaxone.

The National Nosocomial Infections Surveillance system in the United States recently reported that nosocomial infections caused by *Enterobacter* spp. are increasing and a matter of concern (8). This trend has been confirmed all over Europe in the last several years, with *Enterobacter* spp. accounting for 8% of the microorganisms isolated from intensive care units (15).

At this time, there are 13 recognized species in the genus *Enterobacter*. *Enterobacter cloacae* and *Enterobacter aerogenes* are routinely isolated from human clinical specimens, while the other species are mostly isolated from environmental or vegetal sources (5). *Enterobacter cancerogenus* is one of the five new species identified over the last few years. Originally designated enteric group 19 and first ascribed to the genus *Erwinia*, it has been transferred to the genus *Enterobacter* as a senior synonym of *Enterobacter taylorae* when extensive taxonomic investigations revealed its genetic identity to a microorganism identified by Urosĕvić in 1966 and named *Erwinia cancerogena* (6). *E. cancerogenus* is a lactose-fermenting rod. *E. cancerogenus* has a DNA relatedness of 61% to *E. cloacae* and differs from it mostly by being ornithine decarboxylase negative and D-arabinose positive.

E. cancerogenus exhibits natural resistance to aminopenicillins (i.e., amoxicillin and amoxicillin-clavulanic acid) and/or to narrow- and expanded-spectrum cephalosporins (i.e., cefaclor, cefazoline, loracarbef, and cefoxitin). The β-lactam phenotype of *E. cancerogenus* is similar to that expressed by other well-known *Enterobacter* spp. and indicates the presence of chromosomally encoded AmpC β-lactamases (Amber class C β-lactamases) (3, 12, 14).

In agreement with our finding, Pitout et al. found inducible AmpC β-lactamases in all *E. cancerogenus* strains examined ($n = 6$), with isoelectric point (pI) values of >9, suggesting an enzyme similar to those found in the same study in wild-type

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TABLE 1. Review of *E. cancerogenus* infections in humans reported in the literature

Yr	Researchers and reference	No. of patients	Case description[a]	Antibiotic treatment	Outcome
1987	Westblom and Coggins (16)	1	Osteomyelitis of the femur in a 18-yr-old man with an open fracture after a motorcycle accident	Cefotaxime (2 days); cefoperazone (10 days); cefadroxil (2 weeks); cefotaxime (4 weeks); cefotaxime + tobramycin	Chronic infection
1989	Reina et al. (10, 11)	2	Urinary tract infection in a 70-yr-old adult with urinary lithiasis	NA[b]	NA
			Infection of a traumatic cranial wound (car crash) in a 36-yr-old man	NA	NA
1993	Rubinstien et al. (13)	4	Bacteremia and pneumonia in a 75-yr-old man with left ventricular heart dysfunction	Ceftriaxone (7 days); ceftazidime + vancomycin (4 days); tobramycin + vancomycin (4 days)	Died
			Bacteremia, cholangitis, and pneumonia in a 75-yr-old man with adenocarcinoma of the gallbladder	Cefotetan + metronidazole (3 days); trimethoprim-sulfamethoxazole (8 days); ciprofloxacin (10 days)	Died
			Urinary tract infection in a 75-yr-old female with carcinoma of the pancreas	Ampicillin (3 days); ceftazidime + tobramycin	Died
			Urinary tract infection in a 85-yr-old man with benign prostatic hypertrophy and heart disease	Cefuroxime (2 days); clindamycin (2 days); trimethoprim-sulfamethoxazole	Recovered
1994	Martinez et al. (7)	3	Two cases of *E. cancerogenus* infection of an open wound	NA	NA
			One nosocomial bacteremia following prolonged hospitalization	NA	NA
1997	Abbott and Janda (2)	5	Infection of the hand after traumatic cut	Cephradine	Healed
			Infection of the right forearm after open fracture and reduction with plates and screws	Cephradine, gentamicin sulfate	Recovered
			Crushing injury of the left thigh and fracture of the left hip; infected hematoma after surgical treatment	NA	NA
			Multiple trauma with multiple fractures, bacteremia and neck abscess surrounding orthopedic hardware	Tobramycin sulfate	NA
			Multiple trauma with skeletal damage and intracranial injury; infection of a cutdown site in the right safenous vein	Multiple aminoglycosides; penicillin	NA

[a] Most cases have common features: traumatic wounds with environmental source of infection, *E. cancerogenus* isolates resistant to aminopenicillin, initial antibiotic treatment often ineffective, multiple antibiotic regimens, and difficult resolution of infection.
[b] NA, not available.

strains of *E. cloacae* complex (pIs 8.0 to >9) and *E. aerogenes* (pIs 8.4 to 8.8) (9).

The constitutive hyperproduction of AmpC is of major concern, since it confers resistance to most β-lactam antibiotics, sparing only carbapenems and, amongst cephalosporins, only cefepime. This phenotype commonly results from selective antibiotic pressure, and *Enterobacter* isolates resistant to expanded-spectrum cephalosporins are becoming a matter of concern for the possibility of transmitting antibiotic resistance from one microorganism to another worldwide. Outbreaks of infections due to *Klebsiella pneumoniae* harboring plasmid-encoded cephalosporinases and the spread of this resistance mechanism to bacterial species naturally susceptible to cephamycins have been reported (4).

So far, *E. cancerogenus* has been rarely found associated with human infections, and only a few cases of acute or chronic illnesses have been identified: *E. cancerogenus* infections seem to occur mostly in the setting of contaminated wounds, even if other exposures have been reported (Table 1).

The aim of our brief report is primarily to contribute to the understanding of *E. cancerogenus* infections, to the knowledge of the epidemiology, clinical manifestations, and therapeutic options. In this case, the history of an open fracture following a crush injury suggests an environmental, rather than nosocomial, source of the organism: indeed, *E. cancerogenus* is generally recovered from environmental or vegetal sources and is considered mostly phytopathogenic (1). Our strain displayed an antibiotic susceptibility pattern similar to previously reported patterns (10, 11, 13, 16) and was capable of causing the same morbidity as other *Enterobacter* spp. or gram-negative bacteria that cause acute osteomyelitis. Note that this patient had an inappropriate 4-week antibiotic therapy administered before *E. cancerogenus* grew in culture from a swab and the in vitro susceptibility test was available. In conclusion, we suggest that an *E. cancerogenus* infection should be considered in patients with traumatic injuries and secondary infection with a microorganism identified as an *Enterobacter* species, especially when treatment with aminopenicillin is unsuccessful or when wound environmental contamination is plausible.

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