

Severe sepsis from a Ciprofloxacin resistant salmonellosis in a kidney transplant recipient

Sepse grave por salmonelose Ciprofloxacino-resistente em paciente transplantado renal

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ABSTRACT

Introduction: Salmonellosis is a relatively rare complication in kidney transplant recipients that cannot be clinically distinguished from other forms of enteritis. Among kidney transplant patients, it varies broadly in intensity, and is highly associated with extra-intestinal disease, bacteremia, and, in this case, a high mortality rate. **Case Report:** Here we describe a clinical case of ciprofloxacin resistant salmonellosis in a kidney transplant patient. **Conclusion:** This case illustrates how immunosuppressed patients can be exposed to rare forms of infection, often clinically difficult to identify, and possibly with severe clinical courses and poor outcomes despite evidence-based empiric antibiotic therapy.

Keywords: Bacteremia; drug resistance; enterobacteriaceae; immunocompromised host; kidney transplantation; salmonella.

RESUMO

Introdução: A salmonelose é uma complicação relativamente rara em transplantados renais, e não pode ser diferenciada de outras formas de enterite pela apresentação clínica. Em pacientes transplantados renais, a salmonelose varia em gravidade, e é frequentemente associada com formas extra intestinais, bacteremia, e, neste caso, com elevada mortalidade. **Relato de Caso:** Descrevemos o caso clínico de um paciente transplantado renal com salmonelose Ciprofloxacino-resistente. **Conclusão:** Este caso ilustra o risco, relacionado à imunossupressão, da ocorrência de formas raras de infecção, por vezes de difícil diagnóstico, e com cursos clínicos potencialmente graves e prognóstico ruim, apesar do emprego de antibioticoterapia empírica adequada e de acordo com as evidências disponíveis.

Palavras-chave: Bacteremia; enterobacteriaceae; imunossupressão; resistência bacteriana; salmonelose; transplante renal.

INTRODUCTION

Diarrhea is common among kidney transplant recipients (KTR). It has many potential etiologies and varies from mild limited cases to chronic and disabling presentations.¹⁻³ Prevalence of multi-drug resistant gram-negative bacteria may reach 20 to 50% among solid-organ transplant recipients, depending on the studied population.^{4,5} Enteritis caused by *Salmonella sp.* is a rare form of infection that cannot be clinically differentiated from common acute enteritis, and usually responds well to fluoroquinolones.⁶⁻⁸ In immunosuppressed patients, however, it can be more easily associated with bacteremia, and, consequently, to a much worse prognosis.⁹⁻¹¹

In this paper, we present a rare case of invasive diarrhea with severe sepsis caused by ciprofloxacin resistant *Salmonella sp.* in a KTR, and a brief literature review.

CASE REPORT

A 73 year-old, male KTR with a previously well-functioning graft (serum creatinine 1.2 mg/dL), receiving prednisone (5 mg PO every other day), sirolimus (2 mg PO daily) and mofetil mycophenolate (750 mg PO twice a day), was admitted with a 5-day history of asthenia, diffuse abdominal pain and watery non-inflammatory diarrhea, with over 10 evacuations per day. He denied the use of antibiotics for the last 2 years.

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At physical examination, the patient was dehydrated, tachycardic (105 bpm), with orthostatic hypotension (90x50 mmHg), and afebrile. The abdomen was flaccid, with slightly enhanced peristalsis, and no palpable masses. He had been hospitalized for 7 days, six months before, for investigation of a thyroid benign nodule.

Blood routine tests and cultures of blood, urine and stool were collected. Intravenous ciprofloxacin (400 mg every 12 hours) and crystalloid reposition with potassium supplementation were promptly initiated, as the patient showed severe hypokalemia (2.4 mEq/L), increased creatinine (5.5 mg/dL), mild hyponatremia (129 mEq/L), and a left-shifted leukogram (20% band neutrophils). Twenty-four hours after admission, the abdominal pain persisted, and a plain radiograph disclosed ileus, which was attributed to persisting hypokalemia (3.1 mEq/L), dehydration and metabolic acidosis (pH 7.27, HCO₃⁻ 11 mEq/L).

In the second day, the patient experienced an episode of bloody diarrhea. Kidney function (creatinine 6.6 mg/dL) and metabolic acidosis (pH 7.10, HCO₃⁻ 4 mEq/L) worsened and hemodialysis was then started. An exploratory laparotomy was first indicated after an abundant drainage of fecaloid material through a nasogastric tube, but it was later contraindicated based on the very poor clinical condition.

The patient showed an apparent clinical improvement after dialysis, but presented hemodynamic deterioration and cardiac arrest 54 hours after the antibiotic treatment was first initiated. The stool culture, grown in Mac Conkey agar, and conventional blood culture, manually incubated in chocolate agar medium, were available only 24 hours after death, and were both positive for a strain of

Salmonella sp., susceptible only to chloramphenicol and antipseudomonal third and fourth-generation cephalosporins, such as ceftazidime and cefepime, but not to ciprofloxacin, ampicillin and cotrimoxazole. An overview of laboratorial data from this case is displayed in Table 1.

DISCUSSION

We described an atypical case of a 73 year-old KTR, who presented acute invasive diarrhea, and developed a severe sepsis caused by a ciprofloxacin resistant strain of *Salmonella sp.* that could not be effectively treated with standard antibiotic therapy.

Diarrhea is a relatively common complication among KTR, with an incidence of over 20% per year.^{1,2} It is usually mild, self-limited or indolent, and often related to a viral or bacterial infection, use of medications, or to specific immunosuppressant gastro-intestinal toxicity, markedly due to mycophenolic acid preparations.³ An enteritis caused by *Salmonella sp.* cannot be clinically distinguished from those caused by other bacteria, as in both cases the classical symptoms are acute-onset fever, diarrhea and abdominal pain.^{6,7}

The incidence of salmonellosis in KTR is lower than 2% per year.^{6,8} This clinical condition has a broad spectrum of gravity, but in immunocompetent hosts, bacteremia can be seen in less than 5 to 10%. Otherwise, in KTR it is rather common to find an extra-intestinal form of salmonellosis, such as meningitis, osteomyelitis, cholangitis and pneumonia (up to 35%), and bacteremia can be demonstrated in 60 to 70% of cases.⁹⁻¹¹

Bacteremia from *Salmonella sp.* is known to bear a high risk of mortality, as described in a series of

TABLE 1 LABORATORIAL DATA

Data	Admission	24h after admission	48h after admission (before dialysis)	48h after admission (after dialysis)
Creatinine (mg/dL)	5.5	6.5	6.6	2.9
Hemoglobin (g/dL)	11.3	-	10.7	-
Leukocytes (per mm ³)	8,670	-	12,500	-
Band neutrophils (%)	20	-	71	-
Urea (mg/dL)	172	211	229	110
Potassium (mEq/L)	2.4	3.1	3.5	-
Sodium (mEq/L)	129	141	139	136
pH	-	7.27	7.10	7.42
HCO ₃ ⁻ (mEq/L)	-	11	4	18

mg/dL: milligrams per deciliter; g/dL: grams per deciliter; mm³: cubic millimeter; %: percentage of total; mEq/L: milliequivalent per liter.

cases from the Massachusetts General Hospital, in which an outbreak registered in 1990 caused the death of 18% of patients.⁷ Overall, the duration of the infection tends to be longer in KTR, with relapse rates of 43 to 45%, and mortality rates of 5 to 6%.^{6,10}

A literature review with 37 cases of salmonellosis in KTR identified the species of *Salmonella sp.* in 35 patients, with predominance of *S. typhimurium* in 24 cases, *S. panama* in 3 cases, and *S. johannesburg* and *S. enteritidis* in 2 cases each.⁶ In southeastern Brazil, the region where this case was registered, most common serotype is *S. enteritidis* (67.4%), followed by *S. typhimurium*.¹¹

Infections caused by *Salmonella sp.* must be treated with empiric venous antibiotics, preferentially a 14-day scheme consisting of a fluoroquinolone or a third generation cephalosporin, to be initiated after collection of standard blood and stool cultures, which can be grown in chocolate agar, sheep blood agar or Mac Conkey agar media, as appropriate.^{3,7,12}

In cases of *Salmonella sp.*-related bacteremia, the same classes of antibiotics are indicated, but the length of antibiotic therapy must be individualized, as a longer course of antibiotics or a surgical intervention may be needed, due to a higher incidence of relapses observed in immunocompromised hosts, and to the possibility of a source of persistent infection, such as an abscess.^{3,7,12}

The case we described has the peculiarity of presenting a very dramatic form of salmonellosis, caused by a string of *Salmonella sp.*, presenting a broad spectrum of resistance, including ciprofloxacin resistance, which is not common in the literature and could not be timely diagnosed based on cultures, reason for which the initial antibiotic treatment was not changed from ciprofloxacin.¹³

Moreover, the patient did not present any specific risk factors for a ciprofloxacin resistant bacterial infection, such as previous treatment with broad-spectrum antibiotics, prolonged use of any medical device, or a recent prolonged hospital stay, and had been in good clinical condition for a long period, prior to the beginning of the enteritis.¹⁴ Lack of clinical response could not be thoroughly judged, since a period no longer than 48 hours from admission and from the start of antibiotic treatment had passed until the patient showed further clinical deterioration.

The global prevalence of resistant infections caused by Gram-negative bacteria has been increasing in the last years. The same pattern has also been reported in transplant recipients. The most clinically important drug-resistant bacteria reported in transplant patients include non-lactose fermenters such as *Pseudomonas* species, *Burkholderia* species and *Stenotrophomonas* species, carbapenem-resistant *Acinetobacter* species, and multidrug-resistant (MDR) *Enterobacteriaceae*, with carbapenem-resistant *Enterobacteriaceae* being of particular concern. It is worth noting that *Salmonella* species are not included in the group of major concern.¹⁴

Particularly regarding this case, the isolated bacteria, despite a rather broad pattern of resistance, which included ciprofloxacin, retained susceptibility to some antibiotics, such as chloramphenicol, and therefore could not be classified as MDR.¹⁵ Ciprofloxacin-resistant salmonellosis is rather uncommon, though increasingly reported in the literature, and has been suggested to be related to previous use of antibiotics, contactants, or agricultural use of quinolones. The patient, we described here, did not report previous exposure to ciprofloxacin.¹⁵

In conclusion, this ciprofloxacin-resistant pattern rendered the treatment ineffective, and the patient developed an invasive and rapidly lethal form of infection. This case illustrates that rather common manifestations such as diarrhea can correspond to potential life-threatening and rare forms of infection in KTR, and suggests that, in addition to other forms of resistant bacteria, the possibility of ciprofloxacin-resistant salmonellosis should be considered, when initial evidence-based antibiotic therapy does not lead to a clinical improvement within 48 hours of treatment.

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