Severe leptospirosis after a rat bite in an urban setting

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A 76-year-old man presented to the emergency department during the winter in Montréal, Quebec, with a 3-day history of fever, headache and abdominal pain. His abdomen was soft, mental status was preserved, he had no neck stiffness and his skin was normal. No jaundice was observed and his conjunctivae were normal. However, he was hypotensive and tachycardic, without hypoxemia. Eighteen days before admission, the patient had found a rat in his toilet bowl, and it had bitten him on 2 fingers as he tried to remove it. He had consulted the emergency department, where he received basic wound care and a booster dose of tetanus vaccination before being discharged. On his return visit to the emergency department, only mild erythema around the bite wound remained, without purulent discharge. Otherwise, he had had no contact with any other animal, had no sick contact and had not travelled outside the city recently. His medical history included diabetes, and he had a history of a nonsevere allergy to cefazolin. Blood tests showed acute kidney injury and thrombocytopenia. The results of all important laboratory investigations are summarized in Table 1. A computed tomography scan of the abdomen was within normal parameters.

The patient was admitted to the intensive care unit (ICU) for hypotension and multiorgan dysfunction secondary to sepsis of unclear origin. We initiated treatment with aggressive fluid resuscitation and intravenous piperacillin–tazobactam at 3.375 g every 6 hours. He did not require vasopressors as hypotension responded well to fluids. Oxygen saturation levels remained normal. Despite the favourable hemodynamic evolution, the acute kidney injury the patient had had on arrival deteriorated from a creatinine level of 162 μmol/L to 518 μmol/L. He did not meet any criteria for hemodialysis. He also developed severe thrombocytopenia (nadir 17 × 10⁹/L). His liver enzyme levels remained normal.

Given the patient's clinical presentation and history of rat bite, we suspected both leptospirosis and rat-bite fever. We collected and incubated blood culture bottles. We sent leptospirosis serologies and polymerase chain reaction (PCR) tests on urine to the National Microbiology Laboratory in Winnipeg, Manitoba.

Because of the patient's accentuated thrombocytopenia and out-of-proportion acute kidney injury, he received steroids. He also received intravenous immunoglobulin (IVIG) in case there was an immune component to the severe thrombocytopenia.

Key points

- Differential diagnosis of acute undifferentiated febrile illness after a rat bite includes leptospirosis (*Leptospira interrogans*) and rat-bite fever (*Streptobacillus moniliformis* or *Spirillum minus*).

- Diagnosis of leptospirosis can be difficult, as this pathogen cannot be isolated from conventional cultures, and other laboratory investigations are therefore necessary to confirm the diagnosis.

- While test results are pending, penicillins are the antibiotics of choice to treat severe leptospirosis and rat-bite fever, and corticosteroids might also be considered.

- Although antibiotic preventive therapy after a rat bite remains an unresolved issue, rat bites could warrant antibiotic prophylaxis because they regularly result in rat-bite fever, and they create puncture wounds that have a higher risk of infection.

The patient improved over the next few days, with normalization of creatinine level and platelet count, and was discharged from the ICU after 3 days. Steroid weaning began 3 days after treatment initiation. After 7 days of piperacillin–tazobactam, antibiotic treatment was completed with 500 mg oral amoxicillin administered 3 times daily for a total of 14 days.

Leptospirosis was later confirmed on multiple samples. A specific real-time PCR targeting the *LipL32* gene was positive for *Leptospira* sp on the urine specimen. It was then confirmed as *Leptospira interrogans* through conventional PCR and sequencing. The negative blood culture bottles were sent out to Laboratoire de santé publique du Québec, where 16S rRNA PCR and sequencing identified *Leptospira* sp. Serology for *Leptospira* immunoglobulin M taken on day 2 of the patient's hospital stay was negative. We did not perform serology on convalescent serum because a diagnosis had been confirmed, and the patient had received IVIG, which interferes with the test.

Discussion

A careful exposure history is paramount in the clinical approach to acute undifferentiated febrile illness to rule out potential life-threatening infections. Given this patient's history of a bite by a wild urban rat, *L. interrogans* and agents of rat-bite fever had to be considered. Rat-bite fever is predominantly caused by *Streptobacillus moniliformis* in the Americas, whereas *Spirillum minus* causes cases

Table 1: Laboratory results of a 76-year-old male with hypotension and multiorgan dysfunction from leptospirosis from a rat bite 18 days before presentation

Laboratory parameters	Jan. 25: Emergency department	Jan. 26: ICU transfer	Jan. 28: Initiation of IVIG and steroids	Feb. 2: Completion of steroids	Feb. 11: Discharge from hospital	Mar. 15: Follow-up outpatient visit
Hemoglobin (130–165 g/L)	141	114	110	119	103	113
Leukocyte count (4.5–10.8 × 10⁹/L)	8.0	10.8	7.5	6.8	5.3	6.4
Platelets (140–440 × 10⁹/L)	82	23	17	107	156	235
International normalized ratio (0.90–1.20)	1.30	1.47	1.09	1.11		
Creatinine (52–110 μmol/L)	162	338	518	470	180	98
Bilirubin total (0–21 μmol/L)	10	9	8	12	8	
Aspartate aminotransferase (0–40 U/L)	23	32	40			22
Alanine aminotransferase (0–40 U/L)	26	29	31	40	56	30
C-reactive protein (0.0–5.0 mg/L)	300	343	362			
Blood cultures, 2 sets each time	Negative	Negative				
Leptospira immunoglobulin M (NML)		Negative				
16s rRNA PCR with sequencing on blood specimen (LSPQ)	*Leptospira* sp. (Feb. 9*)					
Specific urine PCR (NML)			Positive for *Leptospira* (Feb. 17*), confirmed as *Leptospira interrogans* (Mar. 16*)			

Note: ICU = intensive care unit, IVIG = intravenous immunoglobulin, LSPQ = Laboratoire de santé publique du Québec, NML = National Microbiology Laboratory, PCR = polymerase chain reaction.
*Day on which the result was made available.

in Asia. However, rat-bite fever seemed less likely given the absence of typical maculopapular rash and arthralgias. Sepsis caused by other pathogens from the rat's oral flora (including staphylococci, streptococci, *Pasteurella* and anaerobes) were deemed less likely because there were no local signs of infection at the bite site. Rats can transmit salmonellosis, but it usually occurs through the fecal–oral route. Other less common infections directly or indirectly transmitted by rats (hantavirus, tularemia, plague, murine typhus) were not considered as they are not reported in Montréal.

Leptospirosis is a zoonosis present in every country, but more prevalent in tropical regions, caused by spirochetes of the genus *Leptospira*.[1] Wild mammals, particularly rodents, represent the most important reservoir of *L. interrogans*. They carry it in their renal tubules and shed it in their urine. The bacteria can then survive in water or soil. Human infections typically occur after exposure of mucosa or nonintact skin to contaminated urine or environments. Transmission through animal bites is less common but has been reported.[2] Because rats do not shed leptospires in their saliva, temporary contamination of their oral cavity with urine has been suggested as an explanation for transmission through bites.[3] Liberal use of antibiotics after animal bites could explain the low frequency of bite-related leptospirosis.

The clinical spectrum of leptospirosis ranges from subclinical to fatal. It may follow a biphasic course. The acute leptospiremic phase typically begins 1–2 weeks after exposure and lasts about a week. It usually presents with sudden flu-like symptoms such as fever, headache and myalgias, and sometimes characteristic bilateral conjunctival hyperemia. After initial improvement, a minority of patients develop an immune phase when antibodies develop, with a recurrence of systemic symptoms and sometimes aseptic meningitis. Severe leptospirosis is rare and begins early in the course of the disease. Patients can present in shock, icteric but with only mildly elevated aminotransferases, with disproportionate renal failure, thrombocytopenia and sometimes pulmonary hemorrhage. Mortality rates have been reported to be 5%–15%.[4] The complete pathophysiology is not fully understood, but septic vasculitis could partly explain some of its features. Rat-bite fever can also have a complicated course. Even if most cases resolve spontaneously, untreated infection has a reported mortality of about 10%.[5]

Diagnosis of leptospirosis and rat-bite fever can be challenging because *L. interrogans* and *S. minus* cannot be isolated from conventional cultures. Even if *S. moniliformis* growth is inhibited by sodium polyanethol sulfonate (SPS), the anticoagulant present in aerobic blood culture media, it can be cultured in the anaerobic bottles. If rat-bite fever is suspected, clinicians should contact

Table 2: Antibiotic preventive therapy after an animal bite

Indications for antibiotic prophylaxis in animal bite wounds[7] (based on studies on dog and cat bites):
• Wound on hands, face or genital area
• Wound penetrating the periosteum or the joint capsule
• Deep puncture wound (like a cat bite)
• Wound undergoing primary closure
• Wound in areas with edema
• Wound in host with immunosuppression, asplenia, chronic liver disease or alcoholism

Animal	Pathogens from the oral flora[7,8]	Antibiotic prophylaxis choice (3–5 d)[7]
Cat	*Pasteurella* sp. *Staphylococcus* sp. *Streptococcus* sp. Anaerobes	First choice: • Amoxicillin–clavulanate Alternatives: • Cefuroxime + anaerobic coverage • Doxycycline ± additional anaerobic coverage • TMP-SMX + anaerobic coverage • Moxifloxacin Anaerobic coverage: • Metronidazole or clindamycin
Dog	Same as cat + *Capnocytophaga canimorsus* (risk of severe sepsis in patients with immunosuppression, asplenia, chronic liver disease or alcoholism)	
Rats	*Streptobacillus moniliformis* (Americas) *Spirillum minus* (Asia) *Staphylococcus* sp. Uncommon: *Leptospira interrogans*	No consensus • Some sources suggest penicillin V or doxycycline against rat-bite fever[9] (probably also effective against leptospirosis) • Others suggest large spectrum like amoxicillin-clavulanate to prevent polymicrobial infection as well[10]
Other animals	Infectious diseases consultation suggested. The pathogens in the oral flora are influenced by factors such as:[8] • Animal class (mammals, birds, fish, reptiles and amphibians) • Type of food or prey ingested • Type of water environment (fresh or saltwater) for aquatic animals	

Other considerations:[7]
• Tetanus: give toxoid booster if no vaccination within 10 yr; add tetanus human immunoglobulin if primary vaccine series never completed (or status unknown) and contaminated wound or puncture wound.
• Rabies postexposure prophylaxis: evaluate the risk according to local epidemiology and public health guidance.

Note: TMP-SMX = trimethoprim–sulfamethoxazole.

their microbiology laboratory for advice. Clinicians should also consider putting a higher blood volume in the bottles to overcome SPS inhibition, or performing molecular diagnosis on fluids (e.g., 16S PCR) in culture-negative cases. Leptospirosis is traditionally diagnosed by serology with a microscopic agglutination test on paired serum samples (acute-phase serum obtained at presentation and convalescent-phase sample collected 7–14 d afterward). As with our patient, an initial negative serologic test does not exclude the diagnosis, as antibodies can be undetectable during the acute phase. Leptospirosis is confirmed by a seroconversion, a 4-fold increase in immunoglobulin G titre or a titre of more than 1:800. A titre of more than 1:200 defines a probable case in Canada. Diagnosis can also be made with PCR targeting nucleic acids sequences specific to *Leptospira* sp. Blood PCR is more sensitive in the acute leptospiremic phase, whereas urine PCR becomes more sensitive during the convalescent phase.

Leptospirosis and rat-bite fever should be treated empirically if suspected, like in this case of acute undifferentiated febrile illness after a potential exposure. Doxycycline is usually used to treat outpatients with mild leptospirosis. For severe leptospirosis, penicillin and ceftriaxone are the drugs of choice and are considered equally effective.[4] These antibiotics also constitute the first-line therapy for rat-bite fever. We started our patient on a broad-spectrum antibiotic (piperacillin–tazobactam) because he was septic, then continued it, given it is a penicillin and therefore effective against leptospirosis, and because the confirmation of the diagnosis was delayed. Evidence on steroid use in severe leptospirosis is of low quality. In this case, we introduced steroids to treat the possible leptospirosis-associated vasculitis because of the patient's deteriorating renal function and thrombocytopenia despite an otherwise favourable evolution with fluids and antibiotics. Subsequent improvement of these parameters could also be a result of the antibiotics only.[6] The consultant hematologist administered IVIG to treat potential immune-mediated platelet destruction. Its role in leptospirosis is unknown and routine use is not advised, especially because IVIG prevents a serologic diagnosis.

Guidelines for management of animal bites exist mostly for dog and cat bites, as they are the most studied.[7] These guidelines recommend antibiotic prophylaxis only if the wound is high risk (Table 2); otherwise, the risk of infection is deemed too low. The

3–5 days of antibiotics should offer empiric coverage of the animal's expected polymicrobial oral flora, like with amoxicillin–clavulanate, but alternative antibiotics exist. For other bites, clinicians must extrapolate from the guidelines and consider the animal's particular flora.[8]

In the United States, rat bites represent 1% of the estimated 2 million animal bites annually, and children are often the victims.[5] The role of antibiotic prophylaxis after a rat bite remains unresolved. Because these bites are historically reported to cause rat-bite fever 10% of the time,[5] some recommend penicillin V or doxycycline preventive therapy even if the efficacy is unknown. Trials offer proof of concept that leptospirosis can be prevented with doxycycline prophylaxis in selected patients with high-risk exposure.[11] Because penicillins are effective for leptospirosis treatment, their effect might be extrapolated for leptospirosis prophylaxis. Theoretically, the nature of rat-bite wounds (deep punctures with a small opening) could create a substantial risk for wound infection. However, a small prospective study found a low wound infection rate (2%), whereas other studies describe an infection rate of around 10%,[10] arguing for antibiotic prophylaxis covering the polymicrobial oral flora (e.g., amoxicillin–clavulanate). Given this conflicting data on the risk of infection after a rat bite, further studies would be welcomed, to formulate clear recommendations about antibiotic prophylaxis.

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