

CASES

A lethal case of generalized tetanus

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A 78-year-old Canadian-born woman presented to an emergency department in Hamilton, Ontario, on Sept. 28 with a two-day history of dysphagia. On Sept. 3, the patient had undergone a dental procedure to remove a plate from her mouth. She had been well until Sept. 17, when she had fallen on her driveway and suffered an abrasion to her right forearm, which had been managed at home by her daughter with local wound care. She had then presented to the emergency department on Sept. 19 with pain and swelling in her right arm. A diagnosis of a possible scaphoid fracture had been made and her wrist splinted. She had also been given an injection of tetanus toxoid, 0.5 mL intramuscularly, because she had received her last tetanus booster more than 10 years previously. On Sept. 24, she had returned to the dentist to have a cavity filled. She subsequently presented to the emergency department on Sept. 28 with a two-day history of dysphagia, drooling, difficulty opening her mouth, and face and neck pain.

Her medical history included a right middle cerebral artery territory stroke six years earlier with residual left-sided weakness, type 2 diabetes mellitus, hypertension, dyslipidemia, osteoporosis, cataracts, glaucoma and amputation of the right first toe for diabetic foot infection. She lived independently and had no recent history of travel.

On physical examination, she had a temperature of 37.8°C and was hemodynamically stable. She had a markedly abnormal posture with arched back and hyperextended neck, consistent with opisthotonos, as well as trismus and neck stiffness. The remainder of her neurologic examination showed deficits related to her previous stroke. Cardiovascular, respiratory and abdominal examinations were noncontributory. The right wrist was splinted; there was no abrasion visible on her right forearm and no other areas of skin breakdown. Results of blood tests showed a leukocyte count of 21.9 (normal 4.0–11.0) $\times 10^9/L$ with 20.4 (normal 2.0–7.5) $\times 10^9/L$ neutrophils. The patient's blood glucose level was 6.4 mmol/L. A lumbar puncture was performed,

and the cerebrospinal fluid showed a leukocyte count of 3 (normal 0–5) $\times 10^6/L$, a protein concentration of 0.36 (normal < 0.45) g/L and a glucose concentration of 8.6 (normal 2.2–3.9) mmol/L. Computed tomography of the head and neck did not show a retropharyngeal abscess or an intracranial space-occupying lesion.

A clinical diagnosis of generalized tetanus was made. Metronidazole was started at a dose of 500 mg intravenously every eight hours and continued for seven days. The patient received 6000 U of tetanus immune globulin (TIG) intramuscularly, although not at the site of the earlier abrasion because it was no longer visible. She was admitted to the intensive care unit, where she required intubation and mechanical ventilation. Midazolam and morphine infusions were started for treatment of severe muscle spasms. She had frequent fluctuations in her blood pressure related to autonomic instability and required tracheotomy on Oct. 13. Intractable spasms continued and an infusion of the neuromuscular blocker cisatracurium was started on Oct. 28. On Nov. 28, she received a second dose of tetanus toxoid, and on Dec. 1, she began a five-day trial of magnesium sulfate infusion, with no substantial change in her clinical status. She also received treatment for multiple nosocomial complications throughout her stay in the intensive care unit, including two episodes of central line-associated bloodstream infection and an upper extremity deep vein thrombosis. On Dec. 8, after discussion with the patient's family, active life

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KEY POINTS

- Tetanus is a toxin-mediated disease that is caused by wound contamination with *Clostridium tetani* spores and is characterized clinically by severe muscle spasms.
- Management of tetanus involves multiple interventions aimed at eliminating toxin, controlling symptoms and providing supportive care.
- More than half of all instances of tetanus in the developed world occur in people over the age of 60 years, and a substantial proportion of this age group does not have protective antibodies against tetanus.
- A coordinated public health effort to promote maintenance of up-to-date tetanus vaccination, particularly in this elderly age group, is necessary to prevent future instances of tetanus in Canada.

support was discontinued because of the lack of clinical improvement and poor prognosis for recovery.

Discussion

This was the first fatal instance of tetanus reported to the Public Health Agency of Canada since 1997.¹ This case report highlights the clinical features of generalized tetanus, management challenges that arose during this patient's clinical course and the changing epidemiology of tetanus in the developed world.

Pathogenesis

Clostridium tetani is an anaerobic gram-positive bacillus. Its natural habitat is soil and it is distributed worldwide. Tetanus occurs when a wound is contaminated with *C. tetani* spores; the anaerobic environment of the wound allows the spores to germinate and produce a toxin, tetanospasmin, which is transported to the central nervous system. Tetanospasmin then binds irreversibly to neurons and prevents release of inhibitory neurotransmitters, thereby allowing unopposed motor and autonomic activity.

The most common means of acquiring tetanus is through a contaminated puncture wound, but other risk factors include dental procedures,² surgery, intramuscular injections, intravenous drug use and burns.³

Clinical presentation

There are four clinical manifestations of tetanus, which reflect differences in host factors and site of inoculation (Table 1).³ The spectrum of disease is variable, and a number of severity scores have been developed. The most commonly used is the Ablett classification, which ranges from mild to moderate trismus with no spasms to prolonged spasms with severe autonomic disturbance (Table 2).^{3,4} This patient's tetanus would be classified as grade IV severity, given her refractory spasms, wide fluctuations in blood pressure and frequent tachycardia.

Tetanus is a clinical diagnosis. Wound cultures are frequently negative for *C. tetani*, and there are currently no other diagnostic tests available. The differential diagnosis in a patient who presents with suspected generalized tetanus is relatively short. The only true mimicker of tetanus is strychnine poisoning, which also presents with opisthotonos and trismus, and can be ruled out only with toxicologic testing.

Generalized tetanus must also be distinguished from dystonic reactions to neuroleptic drugs; however, these reactions typically present with lateral head deviation, which is rare in tetanus. Dystonia can be more definitively ruled out by giving a dose of benztropine and observing for resolution of symptoms. Neuroleptic malignant syndrome can present with rigidity and autonomic instability, but unlike tetanus is also characterized by fever and altered mental status.

The other conditions to consider include stiff man syndrome, hypocalcemic tetany, seizures and meningitis, but these can typically be ruled out based on clinical features, laboratory testing or both. The differential diagnosis for trismus as an isolated symptom includes dental or peritonsillar abscess, diphtheria, mumps and mandibular fracture, but these generally will not have the other systemic features associated with tetanus.

Management

Treatment of generalized tetanus involves multiple interventions targeting different therapeutic goals (Table 3).³ Ongoing toxin production should be prevented through aggressive wound care to physically remove bacteria, as well as antimicrobial therapy active against *C. tetani*. A number of antimicrobials have in vitro activity, but metronidazole is generally the drug of choice based on a nonrandomized trial that showed lower mortality rates compared with penicillin,⁵ as well as theoretical concerns regarding the potential toxicity of penicillin to the central nervous system.

The unbound toxin in the body must then be neutralized with human TIG at a dose of 3000 to 6000 U intramuscularly, with observational data suggesting shorter disease course and lower mortality rates as a result.⁶ The optimal route of administration of TIG is unclear. A meta-analysis of 12 clinical trials comparing intrathecal TIG or equine tetanus antitoxin with intramuscular administration showed a mortality benefit of the intrathecal route over intramuscular preparations (relative risk 0.71 [95% confidence interval 0.62–0.81]).⁷ However 7 of the 12 studies used equine tetanus antitoxin, limiting the generalizability of these findings to the developed world

Table 1: Clinical classifications of tetanus³

Classification	Description
Generalized	Begins with trismus and risus sardonicus (spasm of the facial muscles), then proceeds to generalized spasms and opisthotonos
Localized	Muscle rigidity limited to the site of spore inoculation
Cephalic	Form of localized tetanus affecting cranial nerves, often following a head injury
Neonatal	Generalized tetanus in newborns resulting from infection of the umbilical stump

where equine tetanus antitoxin is not used. In addition, there was risk of bias associated with the included trials because of lack of blinding. Thus, TIG is typically administered intramuscularly in developed countries, but further trials are needed to definitively address this question.

Tetanus infection does not confer immunity and the effect of TIG is temporary, so it is recommended to actively immunize the patient with a full course of tetanus toxoid vaccination starting early in the course of illness.¹

Management recommendations for spasms and autonomic dysfunction are based largely on case reports and series.³ Muscle spasms should be treated with intravenous benzodiazepines; alternative treatments for refractory spasticity include baclofen, barbiturates, dantrolene, propofol and long-term neuromuscular blocking agents such as vecuronium. Autonomic dysfunction, particularly sympathetic hyperactivity, is another common clinical feature and can be treated with labetalol or morphine. Considera-

tion can be given to magnesium sulfate infusion, which was shown in a randomized placebo-controlled trial to reduce the need for other drugs to control muscle spasm and cardiovascular instability, but with no difference in mortality or need for mechanical ventilation.⁸ General supportive care should be continued throughout the clinical course, including adequate nutrition and measures to prevent nosocomial complications. With aggressive management, mortality from tetanus is approximately 18%.⁹

In the case presented above, a number of management challenges arose that complicated the patient's clinical course and ultimately contributed to her death. First, generalized tetanus developed in the patient despite documented postexposure prophylaxis with tetanus toxoid after her fall. This may have been due to an unrecognized humoral immune deficiency that would have resulted in suboptimal response to the tetanus toxoid or due to the initial injury being more contaminated than initially suspected.

Table 2: Ablett classification of severity of tetanus

Grade	Clinical features
I	Mild: mild to moderate trismus; general spasticity; no respiratory embarrassment [respiratory distress]; no spasms; little or no dysphagia
II	Moderate: moderate trismus; well-marked rigidity; mild to moderate but short spasms; moderate respiratory embarrassment with an increased respiratory rate greater than 30 [breaths/min]; mild dysphagia
III	Severe: severe trismus; generalized spasticity; reflex prolonged spasms; increased respiratory rate greater than 40 [breaths/min]; apneic spells; severe dysphagia; tachycardia greater than 120 [beats/min]
IV	Very severe: grade III and violent autonomic disturbances involving the cardiovascular system; severe hypertension and tachycardia alternating with relative hypotension and bradycardia, either of which may be persistent

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Table 3: Management of tetanus³

Goal	Treatment
Stop toxin production	<ul style="list-style-type: none"> Wound care, including débridement if necessary Antimicrobial therapy targeting <i>Clostridium tetani</i>
Neutralize unbound toxin	<ul style="list-style-type: none"> Tetanus immune globulin Active immunization with tetanus toxoid
Control of muscle spasms	<ul style="list-style-type: none"> Intravenous benzodiazepines Long-term neuromuscular blockade for refractory tetany
Management of dysautonomia	<ul style="list-style-type: none"> β-blockers, morphine, epidural blockade and/or magnesium sulfate for sympathetic hyperactivity Pacemaker if bradycardic
General supportive measures	<ul style="list-style-type: none"> Intubation and ventilation; consider early tracheotomy Adequate nutrition Prevention of nosocomial complications

Canadian guidelines recommend a dose of TIG in addition to tetanus toxoid for prophylaxis in the setting of wounds that are not clean,¹ but the delay before the patient's initial emergency department presentation may have masked the fact that the wound was contaminated. Second, she had a protracted clinical course, which we hypothesize was related to her age, comorbidities and early onset of autonomic instability. Finally, the patient developed serial nosocomial complications related to her prolonged hospital stay.

Prevention

The incidence of tetanus has declined substantially since the introduction of the tetanus toxoid vaccine in the 1940s, and fewer than 10 instances per year are seen in Canada.¹ The epidemiology of tetanus in the developed world has changed such that more than half of instances now occur in patients over the age of 60 years,¹

as in our patient. Tetanus immunity is known to wane with age; in Canada, only 58.2% of blood donors over the age of 60 years have protective antibodies against tetanus.¹⁰ Older patients thus represent an emerging risk group for tetanus in the developed world. Current recommendations are that Canadians receive primary tetanus immunization in childhood, followed by boosters every 10 years.¹ There are a number of tetanus toxoid preparations available in Canada, but most adults receive the tetanus and diphtheria adsorbed vaccine.

This case report emphasizes the importance of regular tetanus boosters during adulthood in accordance with guidelines. Tetanus likely would not have occurred in this patient if her booster series had been up to date. A coordinated public health effort to promote maintenance of up-to-date tetanus vaccination, particularly in this older age group, could prevent future instances of tetanus in Canada.

References

1. Public Health Agency of Canada. *Canadian immunization guide*. Ottawa (ON): The Agency; 2006.
2. Burgess JA, Wambaugh GW, Koczarski MJ. Reviewing cephalic tetanus. *J Am Dent Assoc* 1992;123:67-70.
3. Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. *Br J Anaesth* 2001;87:477-87.
4. Ablett JLL. Analysis and main experiences in 82 patients treated in the Leeds Tetanus Unit. In: Ellis M, editor. *Symposium on tetanus in Great Britain*. Boston Spa (UK): National Lending Library; 1967. p. 1-10.
5. Ahmadsyah I, Salim A. Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole. *Br Med J (Clin Res Ed)* 1985;291:648-50.
6. Blake PA, Feldman RA, Buchanan TM, et al. Serologic therapy of tetanus in the United States, 1965-71. *JAMA* 1976;235:42-4.
7. Kabura L, Ilibagiza D, Menten J, et al. Intrathecal vs. intramuscular administration of human antitetanus immunoglobulin or equine tetanus antitoxin in the treatment of tetanus: a meta-analysis. *Trop Med Int Health* 2006;11:1075-81.
8. Thwaites CL, Yen LM, Loan HT, et al. Magnesium sulphate for treatment of severe tetanus: a randomized controlled trial. *Lancet* 2006;368:1436-43.
9. Pascual FB, McGinley EL, Zanardi LR, et al. Tetanus surveillance — United States, 1998-2000. *MMWR Surveill Summ* 2003;52:1-8.
10. Yuan L, Lau W, Thipphawong J, et al. Diphtheria and tetanus immunity among blood donors in Toronto. *CMAJ* 1997;156:985-90.

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