Am. J. Trop. Med. Hyg., 77(2), 2007, pp. 400–402

Case Report: Tetanus-Induced Acute Kidney Injury in a Renal Transplant Recipient

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Abstract. A 48-year-old renal transplant recipient who developed tetanus 6 years after transplantation is described. His immunosuppressive protocol was mofetil mycophenolate, sirolimus, and prednisone. The patient presented symptoms of severe tetanus with autonomic dysfunction, requiring ICU care and mechanical ventilation. His clinical course was marked by development of tetanus-induced acute kidney injury and sepsis. He was discharged after 37 days of hospitalization with recovered renal function. Tetanus is a preventable disease associated with a high fatality rate. Its treatment is difficult and requires specialized and intensive care. This case highlights the crucial importance of following adequate immunization guidelines in transplant recipients.

INTRODUCTION

Tetanus is a highly lethal infectious disease caused by a neurotoxin produced by the gram-positive anaerobic bacillus *Clostridium tetani*. Its clinical picture is caused by over activity of somatic motor neurons induced by the exotoxin. Although rare in developed countries, tetanus remains a health problem in developing countries. There are very few reports of tetanus in solid organ[1] or bone marrow transplantation.[2] We report a case of tetanus-induced acute kidney injury (AKI) in a renal transplant recipient.

CASE REPORT

A 48-year-old male was admitted to the Hospital de Base, São Jose do Rio Preto Medical School, Brazil, with thoracic pain and progressive muscle spasm in the left leg, starting the previous day. He reported to have had a trauma caused by a piece of wood penetrating his right hand 10 days before hospitalization. The patient had undergone living related renal transplantation 6 years ago, and he was receiving an immunosuppressive regimen consisting of mofetil mycophenolate (2.0 g), sirolimus (2.0 mg), and prednisone (10 mg) daily. At the time of hospitalization, his allograft function had been stable and his serum creatinine level was 1.7 mg/dL. Diagnosis of chronic allograft dysfunction had been made previously.

On admission, he was alert and oriented, with trismus and somatic muscle spasm. There was a laceration–contusion wound in the right hand. History of tetanus immunization booster was uncertain. His axillary temperature was 37.3°C, blood pressure was 130/80 mm of Hg, and heart rate was 92 beats/min. The rest of the physical examination was unremarkable. Laboratory evaluation disclosed hemoglobin 12.8 g/dL, hematocrit 40%, leukocytes 10,100/mm^3, platelets 263,000/mm^3, creatinine 2.1 mg/dL, BUN 21 mg/dL, sodium 145 mEq/L, potassium 3.5 mEq/L, pH 7.28, P_{O2} 83 mm of Hg, P_{CO2} 41 mm of Hg, HCO_3 19 mEq/L, glucose 81 mg/dL, and CPK 618 IU/L.

A clinical diagnosis of tetanus was established, and the patient was submitted to surgical investigation and debridement of the wound, where a wood fragment of 1 cm was found. He was transferred to the ICU, and therapy with diazepam, pancuronium, clindamycin, and mechanical ventilation was started. Tetanus immunization and intramuscular antitetanus human immunoglobulin (5,000 IU) were administered. Sirolimus and mofetil mycophenolate were discontinued. His clinical course was characterized by sympathetic nervous system hyperactivity, with wide variations in heart rate and blood pressure, but there was no need for use of vasoactive drugs. On day 3 of hospitalization, despite presenting with diuresis of 3,100 mL, his renal function deteriorated and serum creatinine increased to 2.7 mg/dL, BUN 28 mg/dL, and CPK levels reached 1,171 IU/L. On hospitalization day 9, the patient developed sepsis due to pneumonia. He received recombinant human activated protein C, and the antibiotic therapy was changed to vancomycin plus ampicillin/sulbactam and subsequently to imipenem. There was progressive clinical improvement and cessation of muscle spasms. On hospitalization day 19, pancuronium was withdrawn, and 3 days later sedation was discontinued. On hospitalization day 24, mechanical ventilation was no longer required and he was discharged from the ICU with creatinine level of 1.5 mg/dL. After 37 days of hospitalization, immunosuppression was resumed and the patient was discharged from the hospital.

DISCUSSION

The annual worldwide number of reported accidental tetanus cases has fallen from over 100,000 in 1980 to 15,516 cases in 2005.[3] This dramatic fall in reported tetanus incidence is likely related to the increasing coverage immunization programs, particularly in the developed countries. In the United States during 1998–2000, 43 cases of tetanus were reported annually, on average; the average annual incidence was 0.16 cases/million population, with mortality of 18%.[4] In England and Wales, a total of 175 cases of tetanus were reported during 1984–2000, giving an annual incidence of 0.20 cases per million population.[5] Nonetheless, a true global incidence of 1,000,000 annual cases of tetanus is estimated to occur worldwide, mainly in developing countries[6] and the WHO estimated the occurrence of 290,000 deaths due to tetanus in 2000–2003.[3] In Brazil, 1,548 cases were reported in 1990 and 450 in 2004 (incidence of 0.24 per 100,000 population).[7] Tetanus mortality remains elevated in developing countries, reaching up to 35% in Brazil.[8] Many factors have been related to the fatality rate in tetanus, such as severity of the illness, short incubation and progression times, injection drug use, tachycardia, body temperature over 40°C, and presence of cardiovascular, pulmonary, and renal complications. In the present case, the patient had several poor prognosis factors:

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short incubation time (10 days), short progression time (24 hours), autonomic hyperactivity, sepsis, and acute kidney injury.

Under anaerobic conditions, *Clostridium tetani* spores germinate and produce tetanospasmin. The toxin moves from the contaminated site via the lymphogenic and hematogenic routes to the spinal cord in 2–14 days and then progresses to the brain stem via retrograde axonal transport. Tetanospasmin binds irreversibly to neuronal cells and blocks neurotransmission, disinhibiting neurons that modulate excitatory impulses from the motor cortex. This results into progressively more intense muscle spasms, increased muscular tone and muscle rigidity. Impaired neuronal control of catecholamines released by the adrenals produces autonomic instability clinically expressed as wide variations in heart rate and blood pressure.[9] Tetanus symptoms can start a few days after the infection or be delayed to months later. Usually the incubation period is ≈7 days, as seen in the described patient, and seldom occurs later than 1 month or < 2 days after the causal injury.[10]

Acute kidney injury (AKI) is a frequent and lethal complication of tetanus. In a series of 106 patients with tetanus, 21.7% presented AKI, with a mortality of 65% in contrast to a mortality of 18% in patients with normal renal function.[11] In a retrospective study of 101 consecutive cases of tetanus, 43% developed AKI, with a 73% mortality ratio, in sharp contrast to mortality of 7% in patients with preserved renal function.[12] A recent multivariate analysis of 236 ICU tetanus patients disclosed a direct association between AKI and tetanus mortality.[13] Although many factors, like hypovolemia, presence of sepsis, rhabdomyolysis, use of nephrotoxic drugs, and mechanical ventilation-induced impaired cardiac output, might cause renal injury in tetanus, the key mechanism for tetanus-induced AKI is likely autonomic overactivity, a characteristic feature of severe tetanus.[11,12,14] Alternate episodes of tachycardia and bradycardia, hypertension and hypotension, hyperthermia, bronchic hypersecretion, and profuse sudoresis are frequent in the second week of disease in these patients. The large variations in blood pressure and vascular tonus caused by catecholamine release and autonomic nervous system exhaustion can impair renal hemodynamics. Daher and others, in a prospective study of 30 tetanus patients, demonstrated early and intense autonomic system overactivity in the group developing renal impairment. Use of nephrotoxic drugs, need for mechanical ventilation, presence of sepsis, creatine phosphokinase levels, and myoglobinuria were similar in patients developing AKI and those with normal renal function.[15]

Patients at risk for tetanus are those who did not receive of a full series of tetanus toxoid immunization or those who did not receive a booster dose at the correct time (every 10 years after immunization). Even in developed countries, a substantial number of adult individuals are not effectively immunized. McQuillan and others, analyzing a cross-sectional sample of 18,045 persons 6 years of age or older in the United States, found that only 72% of the group presented fully protective levels of antitetanus antibody. When adults > 70 years old were analyzed separately, this percentage dropped to 31%.[16] In another recent survey, only 6% of the patients with tetanus reported to the U.S. Centers for Disease Control and Prevention from 1998 to 2000 were up-to-date with their tetanus vaccination.[4] Although scarce, the available data suggested that chronic renal disease patients have an impaired response to primary tetanus vaccination[17] and that the antibody titles might decrease below protection levels 5 years after the primary vaccination in hemodialysis patients.[18] In the same way, data about transplant patients are limited. Theoretically, immunosuppressive drugs could cause less seroconversion and lower antibody levels after immunization. Huzly and others compared 164 renal transplant recipients with healthy controls before and after tetanus vaccination. Although prebooster tetanus antitoxin values were lower in transplant recipients, all patients developed protective tetanus antibody levels that remained effective for at least 1 year after immunization. There were no rejection episodes and renal function remained stable after immunization, suggesting that tetanus vaccination is safe in this population.[19] The most reasonable current recommendation for renal transplantation patients is to routinely administer tetanus boosters at regular intervals and assess postvaccination titers every 5 years.[20]

Only 2 cases of tetanus in transplant recipients have been previously reported in the medical literature. In the first, a bone marrow transplant patient developed tetanus symptoms 54 days after transplantation. His immunosuppressive regimen was composed of total body irradiation, cyclophosphamide, cyclosporin, and methylprednisolone. The patient developed respiratory failure and AKI and died 14 days after onset of tetanus symptoms. Six years before transplantation, he sustained an open fracture with a delayed pin-and-plate insertion. At the time, an antitetanus immunization booster was administered.[2] In the only case of tetanus in a renal transplant recipient previously described, the patient developed the disease 12 years after the transplantation, even though he presented circulating tetanus antibodies in a level considered protective. He was receiving azathioprine, prednisone, and cyclosporine. His history of vaccination was doubtful. The patient had a favorable clinical course, without need for mechanical ventilation or deterioration of renal function.[1] To our knowledge, the present case is the first report of tetanus in renal transplant recipients under sirolimus and mofetil mycophenolate therapy. Both drugs are potent immunosuppressants that have antiproliferative properties and interfere at different steps of the cellular cycle. When co-administered, their effects may be amplified. In the described case, it is possible that this combination might have played a role in the development of the tetanus.[21]

Tetanus is a preventable disease associated with a high fatality rate. Its treatment is difficult and requires specialized and intensive care. The described case calls attention to the crucial importance of performing routine immunizations in transplant recipients according to established guidelines.

Received February 28, 2007. Accepted for publication April 18, 2007.

Financial support: Dr. Emmanuel A. Burdmann was partially supported by a grant from CNPq, Brazil (301034/2003-6).

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REFERENCES

1. de La Chapelle A, Lavabre O, Pinsard M, Delamonica J, Relyveld EH, 2002. Tetanus in a renal transplant recipient exhib-

iting the presence of circulating antitetanus antibodies determined by ELISA. *Biomed Pharmacother 56:* 208–210.
2. Kendra JR, Halil O, Barret AJ, Selwyn S, 1982. Tetanus after allogenic bone marrow transplantation. *Br Med J 285:* 1393–1394.
3. World Health Organization, 2006. *Tetanus*. Geneva: WHO.
4. Pascual FB, McGinley EL, Zanardi LR, Cortese MM, Murphy TV, 2003. Tetanus surveillance—United States, 1998–2000. *MMWR Surveill Summ 52:* 1–8.
5. Rushdy AA, White JM, Ramsay ME, Crowcroft NS, 2003. Tetanus in England and Wales, 1984–2000. *Epidemiol Infect 130:* 71–77.
6. Thwaites CL, Farrar JJ, 2003. Preventing and treating tetanus. *BMJ 326:* 117–118.
7. Ministry of Health Brazil, 2006. *DATASUS*. Brasília, DF, Brazil: Ministry of Health Brazil. Available at: www.datasus.gov.br.
8. Greco JB, Tavares-Neto J, Greco JB Jr, 2003. Accidental tetanus: prognosis evaluation in a historical series at a hospital in Salvador, Bahia, Brazil. *Rev Inst Med Trop Sao Paulo 45:* 35–40.
9. Farrar JJ, Yen LM, Cook T, Fairweather N, Binh N, Parry J, Parry CM, 2000. Tetanus. *J Neurol Neurosurg Psychiatry 69:* 292–301.
10. Vandelaer J, Birmingham M, Gasse F, Kurian M, Shaw C, Garnier S, 2003. Tetanus in developing countries: an update on the Maternal and Neonatal Tetanus Elimination Initiative. *Vaccine 21:* 3442–3445.
11. Seedat YK, Omar MA, Wesley A, Pather M, 1981. Renal failure in tetanus. *Br Med J 282:* 360–361.
12. Burdmann E, Daher E, Motti E, Malheiro P, Abdulkader R, Silva JC Jr, Sabbaga E, Marcondes M, 1989. Etiopathogenesis of acute renal failure (ARF) related to tetanus. *Ren Fail 11:* 52.
13. Brauner JS, Rios Vieira SR, Bleck TP, 2002. Changes in severe accidental tetanus mortality in the ICU during two decades in Brazil. *Intensive Care Med 28:* 930–935.
14. Hariparsad D, Pather M, Rocke DA, Wesley AG, 1984. Renal function in tetanus. *Intensive Care Med 10:* 67–70.
15. Daher EF, Abdulksder RCRM, Motti E, Marcondes M, Sabbaga E, Burdmann EA, 1997. Prospective study of tetanus-induced acute renal dysfunction: role of adrenergic overactivity. *Am J Trop Med Hyg 57:* 610–614.
16. McQuillan GM, Kruszon-Moran D, Deforest A, Chu SY, Wharton M, 2002. Serologic immunity to diphtheria and tetanus in the United States. *Ann Intern Med 136:* 660–666.
17. Girndt M, Pietsch M, Kohler H, 1995. Tetanus immunization and its association to hepatitis B vaccination in patients with chronic renal failure. *Am J Kidney Dis 26:* 454–460.
18. Kruger S, Muller-Steinhardt M, Kirchner H, Kreft B, 2001. A 5-year follow-up on antibody response after diphtheria and tetanus vaccination in hemodialysis patients. *Am J Kidney Dis 38:* 1264–1270.
19. Huzly D, Neifer S, Reinke S, Schroder K, Schonfeld C, Hofmann T, Bienzle U, 1997. Routine immunizations in adult renal transplant recipients. *Transplantation 63:* 839–845.
20. Duchini A, Goss JA, Karpen S, Pockros PJ, 2003. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. *Clin Microbiol Rev 16:* 357–364.
21. Grinyo JM, Cruzado JM, 2006. Mycophenolate mofetil and sirolimus combination in renal transplantation. *Am J Transplant 6:* 1991–1999.