



Diagnosis of Tetanus Assisted by Next-Generation Sequencing Analysis of Etiology: A Case Report

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Abstract

Background: Tetanus is a rare surgical infectious disease with a high mortality especially in severe tetanus with autonomic instability. However, tetanus may prove to be difficult to be diagnosed for the rarity of tetanus and the difficulty of cultivation of *Clostridium tetani*. Herein, we reported the first case of diagnosis assistant by next-generation sequencing analysis of etiology.

Case Report: A 50-year-old male patient was admitted to our hospital 10 days after the right arm injury due to pain and masticatory weakness. The pathogen of wound secretion was confirmed to be clostridium tetanus by next-generation sequencing analysis of etiology. The patient's condition rapidly progressed to a severe state with autonomic instability. The patient finally recovered and discharged after surgical debridement twice and comprehensive treatment in ICU, including deep analgesia and sedation with dexmedetomidine.

Conclusion: The diagnosis of tetanus is very rare. We reported a case of severe tetanus diagnosed assistant by next-generation sequencing analysis of etiology and finally successful treatment of his autonomic instability with dexmedetomidine. This case suggested that early diagnosis and reasonable intervention of severe tetanus could reduce mortality.

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Keywords: Tetanus; Next-Generation Sequencing (NGS); Autonomic instability; Dexmedetomidine; Prognosis

Background

Tetanus is a rare fatal infectious disease caused by *Clostridium tetani* [1,2]. Tetanus is characterized by muscle spasm of masticatory muscles first. With the progress of the disease, mild stimulation can trigger generalized tonic epileptic activity, which can lead to fatal clinical manifestations, such as autonomic instability [3,4]. Tetanus is still an endemic epidemic in developing countries, and its incidence rate often rises after natural disasters such as earthquake and tsunami [5]. Most physicians in developed countries lack experience in treating such cases. The treatment of tetanus is not standardized either. By consulting journals and scientific literature, we found that there are few literatures related to the diagnosis or treatment of autonomic instability [7,8]. Therefore, this case report is of great significance for treating doctors in Emergency Department or Intensive Care Units to learn features of tetanus for early recognition and treatment.

Case Presentation

A 50-year-old male building worker presented in our hospital with recent onset of difficulty in opening mouth. The man's right arm was injured at work 10 days before. The local hospital surgeons had already given him surgical debridement and tetanus antitoxin immunotherapy. A 10 cm longitudinal incision was seen on the palmar side of his right forearm. The wound seemed healed well apparently and the stitches had been removed. He represented to our hospital and complained about the difficulty of opening his mouth. He had not received any tetanus vaccinations before. After admission, he was diagnosed tetanus and transferred to a Surgical Intensive Care Unit (SICU) single ward immediately to reduce sound and light stimulation. To neutralize the toxin, 1000 U of



Figure 1: Intraoperative debridement picture (arrow shown building cement sands).

human anti-tetanus immunoglobulin was administered, along with the tetanus toxoid injection. For muscle spasm, diazepam infusion of 1 mg/kg/day was given. Penicillin and metronidazole were given as antibiotic coverage. He developed respiratory failure the following day, these verity of his illness required mechanical ventilation and subsequent tracheostomy. Further surgical debridement was performed the third day after admission and 1000 IU of tetanus immunoglobulin was injected intramuscularly around the wound. It was confirmed that the first debridement was not complete, and residual building cement sands were found in the wound (Figure 1). *Clostridium tetani* was identified in wound secretions by Next-Generation Sequencing (NGS) analysis of etiology (Figure 2). The wound was kept open and then washed with hydrogen peroxide every day for almost 10 days. The wound was sutured 18 days later. One week after admission, the man developed autonomic instability symptoms, characterized by high fever, sweating, extreme fluctuations in heart rate and blood pressure. Large doses of neuro-blockers, analgesics and sedatives were administered. His antibiotic regimen altered to intravenous metronidazole and ceftriaxone soon. His gastrointestinal function was weakened and his stomach was seriously reserved. He changed to pyloric feeding later to strengthen nutritional support. We assessed the severity of his tetanus using the Ablett classification [6]; all symptoms were in the very severe category. Recognition of the tetanus pathophysiology, comprehensive treatment in ICU and choice of sedative medications, including dexmedetomidine for 14 days with its anti-sympathetic effect, led to successful discharge. The patient was discharged after 28 days in SICU and 15 days more in respiratory ward. Except for a little stiffness in the joints, the man had clear mind, fluent speech and free movement of joints at the time of discharge. After discharge, the family members complained that the man had an involuntary shaking of left leg when sleeping at night and then head MRI showed multiple ischemic lesions in his right frontal lobe and bilateral parietal lobes. Within 3 months after discharge, this kind of left leg involuntary shaking had always existed.

Discussion and Conclusion

In recent years, no relevant literature has reported the incidence of tetanus in China, but it often happens [7]. Diagnosis of tetanus is mainly based on clinical signs and symptoms. The rarity of tetanus and the difficulty of cultivation of *Clostridium tetani*, which lead to early clinical diagnosis mainly relying on the experience of doctors [1]. However, it is important to realize that tetanus can occur despite

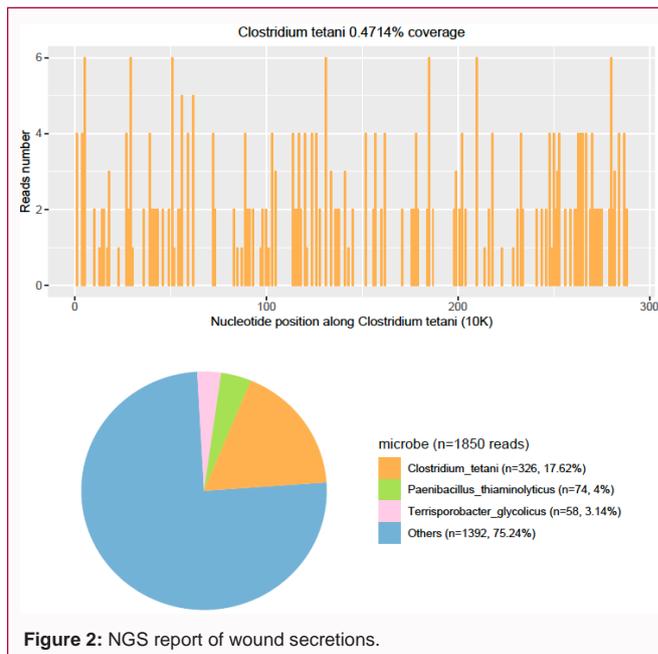


Figure 2: NGS report of wound secretions.

previous immunization and protective anti-tetanus antibody levels. Recently, NGS has shown an advantage in etiological diagnosis. The NGS technology allows for the detection and identification of ('difficult-to culture') microorganisms using a culture-independent strategy [8], especially in the diagnosis of unexplained encephalitis [9,10]. We report a case of tetanus confirmed by NGS sequencing, suggesting that there are still many possibilities in the etiological diagnosis of tetanus. After consulting the literature, we used NGS method to diagnose tetanus for the first time. Autonomic instability is one of the most challenging factors in the treatment of severe tetanus and a circulatory disturbance is one of the common causes of death in severe tetanus [3]. This period is extremely labile and is characterized by malignant hypertension and tachycardia, followed by profound hypotension and bradycardia [3,11]. The optimal treatment for autonomic instability is still unclear [4,12]. Sedatives used range from benzodiazepines such as midazolam and diazepam to anesthetics such as propofol and ketamine. Magnesium sulfate, intrathecal baclofen, morphine, bupivacaine, fentanyl and labetalol can also reduce autonomic instability. However, the evidence is limited to case reports and a few case series [13]. To date, there have been no large-scale studies aimed at identifying specific preferences for the treatment of tetanus related autonomic symptoms. Dexmedetomidine is a more selective α_2 -adrenoreceptor agonist than clonidine. It has combined analgesic and anti-sympathetic effect, make it sensible to consider in this setting [3]. Here we present a case of generalized tetanus complicated by autonomic crises managed with dexmedetomidine infusion about for 14 days. The administration of dexmedetomidine reduced the use of sedative drugs to control muscle spasms and cardiovascular instability. There is no upper limit in dose or frequency of sedative agents. This case illustrates that very high doses of all sedatives were required for almost 3 weeks. We still don't know whether the limb shaking in sleep, the denaturation in the head MRI and tetanus toxin were related. Finally, we should not detract from the importance of general ICU management in treating severe tetanus. Appropriate wound care and debridement, antibiotics and the administration of antitoxin are all essential [7,14]. Also, as tetanus infection does not lead to development of protective antibodies,

immunization with tetanus toxoid is mandatory, as it will reduce the chances of developing tetanus from subsequent wounds [15]. In summary, this case suggested that early diagnosis and reasonable intervention of severe tetanus could reduce mortality. This case also shows that the comprehensive treatment in ICU is very important for the treatment of severe tetanus.

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