

Keberhasilan Pengobatan Tetanus Generalisata Berat dengan Spasme Refrakter dan Koinfeksi Pneumonia Pseudomonas aeruginosa: Laporan Kasus

Successful Treatment of Severe Generalized Tetanus with Refractory Spasm and Pseudomonas aeruginosa Pneumonia Co-infection: A Case Report

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Article Info

Article History:

Received: March 22, 2024

Accepted: May 30, 2024

Published: June 23, 2024

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How to cite this article:

Putri, K. Y. W., Fardhani, I. M., & Rayyan, M. I. R. (2024). Successful Treatment of Severe Generalized Tetanus with Refractory Spasm and Pseudomonas aeruginosa Pneumonia Co-infection: A Case Report. *Journal of Agromedicine and Medical Sciences*. 10(2), 84-88.

<https://doi.org/10.19184/ams.v10i2.47191>

Abstrak

Tetanus merupakan penyakit menular dengan tingkat mortalitas tinggi yang disebabkan oleh bakteri *Clostridium tetani*. Meski dapat dicegah melalui vaksinasi, tetanus masih menjadi masalah yang signifikan terutama di negara berkembang sehingga diperlukan penanganan yang komprehensif untuk mencegah komplikasi yang lebih fatal. Seorang pasien laki-laki berusia 52 tahun, dirujuk ke Instalasi Gawat Darurat rumah sakit kami dengan kekakuan pada rahang, leher, dan perut sejak tiga hari yang lalu. Pasien didiagnosis dengan tetanus setelah terkena duri pohon dan mengalami risus sardonicus, trismus dan opisthotonus yang tidak dapat terkontrol dengan pemberian agen benzodiazepin. Pasien mengalami disfungsi otonom sehingga menyebabkan bradikardia, takikardia, dan tekanan darah yang berfluktuasi. Pasien dirawat selama lebih dari 30 hari di unit perawatan intensif dengan ventilator mekanis, imunoglobulin, antibiotik, antispasme, dan obat sedatif. Selain itu, pasien juga terinfeksi pneumonia *Pseudomonas aeruginosa* selama masa pengobatan. Akhirnya pasien berhasil diobati dan dipulangkan. Laporan kasus ini menyoroti pentingnya perawatan multidisiplin di ICU dalam diagnosis dan terapi dari pasien tetanus, yang diharapkan dapat memberikan luaran terbaik bagi pasien.

Kata Kunci: laporan kasus; spasme refrakter; tetanus generalisata; penyakit neuroinfeksi; pneumonia

Abstract

Tetanus is an infectious disease with a high mortality rate caused by the bacterium *Clostridium tetani*. Although it can be prevented through vaccination, tetanus is still a significant problem, especially in developing countries, so comprehensive treatment is needed to prevent more fatal complications. A 52-year-old male patient was referred to our hospital's Emergency Department with stiffness of the jaw, neck and abdomen three days ago. The patient was diagnosed with tetanus after being hit by a tree thorn and developed risus sardonicus, trismus, and opisthotonus, which could not be controlled with benzodiazepines. The patient developed autonomic dysfunction, resulting in bradycardia, tachycardia, and fluctuating blood pressure. The patient was treated for more than 30 days in the intensive care unit with a mechanical ventilator, immunoglobulin, antibiotics, anti-spasm, and sedatives. In addition, the patient was also infected with *Pseudomonas aeruginosa* pneumonia during the treatment period. Finally, the patient was successfully treated and discharged. This case report highlights the importance of multidisciplinary care in the ICU in diagnosing and treating tetanus patients, which is expected to provide the best outcomes for patients.

Keywords: case report; refractory spasm; generalized tetanus; neuroinfectious disease; pneumonia.



Introduction

Tetanus is a disease of the neuromuscular system caused by neurotoxins originating from the bacterium *Clostridium tetani* with symptoms of spasms and muscle stiffness without impaired consciousness. Moreover, the neurotoxins of tetanus are not limited to the motor system, as autonomic dysfunction is joint in generalized tetanus, with episodes of tachycardia, hypertension, and sweating, sometimes alternating with bradycardia and hypotension. Although this disease can be prevented through vaccination, tetanus is still a cause of high mortality in countries with low income and limited resources (Dong et al., 2019; Karnad & Gupta, 2021; Sanchez-Grillo et al., 2023). Some complications due to tetanus include pneumonia, laryngospasm or respiratory muscle spasms, vertebral fractures, rhabdomyolysis, and severe autonomic dysfunction (Almas et al., 2021; Bae & Bourget, 2023). Complications in tetanus patients are life-threatening and must be treated immediately and appropriately. This article presents a case of a 52-year-old man with severe generalized tetanus accompanied by autonomic dysfunction, refractory spasm, and *Pseudomonas aeruginosa* pneumonia co-infection that has been successfully managed appropriately after undergoing therapy for more than one month (33 days) in the hospital.

Case Report

A 52-year-old man with a farming background was referred to our hospital's Emergency Department with the main complaint of stiffness in the jaw, neck, and stomach three days before admission. The patient was diagnosed with generalized tetanus based on the patient's clinical history. Based on hetero-anamnesis with the patient's family, the patient previously had a history of being pricked by a thorn tree on his right toe one week ago. The patient was treated for three days in the hospital's Intensive Care Unit (ICU) due to continuous muscle spasms. The patient's family denied any history of previous comorbidities, and they did not know the patient's tetanus immunization status. On admission, the patient was placed on a mechanical ventilator and sedated with midazolam 3 mg/hour, morphine 1 mg/hour, and diazepam 2 mg/hour as an antispasm. Installation of a ventilator to prevent airway spasms, respiratory depression, and autonomic dysfunction, which are at risk of severe tetanus. The patient had previously received human tetanus immunoglobulin (HTIG), Tetagam® 3000 IU and intravenous antibiotics with metronidazole 500 mg four times daily and ceftriaxone 1 gram twice daily as the drug of choice. On initial examination, vital signs were found: blood pressure 111/60 mmHg, respiratory rate 16 breaths/minute, pulse 90 beats/minute, and body temperature 38.2 °C. Physical examination revealed risus sardonicus, trismus, and opisthotonus. Then, the patients were treated in an isolation room in the ICU that was dark and quiet and with minimal external stimulation to prevent spasms due to sensitization. Laboratory examination results on the first day of treatment showed hemoglobin 11.3 g/dL (13.5-17.5 g/dL), leukocytes $8.9 \times 10^3/\mu\text{L}$ ($4.5-11 \times 10^3/\mu\text{L}$), platelets $182 \times 10^3/\mu\text{L}$ ($150-450 \times 10^3/\mu\text{L}$), sodium 142 mmol/L (135-155 mmol/L), potassium 4.22 mmol/L (3.5-5 mmol/L), magnesium 0.54 mmol/L (0.73-1.06 mmol/L), calcium 1.88 mmol/L (2.15-2.57

mmol/L), urea 71 mg/dL (12-43 mg/dL), creatinine 1 mg/dL (0.6-1.3 mg/dL), and BUN 33 mg/dL (6-20 mg/dL). Due to indications of the need for a long-term ventilator, the following day, the patient was planned to undergo an elective tracheostomy. Patients are given additional magnesium sulfate (MgSO₄) infusion at 0.8 grams/hour to prevent spasms and autonomic dysfunction. Administration of MgSO₄ can affect the electrolyte panel, especially calcium. Therefore, the patient was also given additional calcium gluconate 2 grams and CaCO₃ 500 mg, each thrice daily. Because he was still experiencing spasms, the patient was given a further 30-60 mg of propofol every time a spasm occurred. He continued with the administration via a pump at 30 mg/hour. Even though he had been given a combination of benzodiazepine agents, MgSO₄, and propofol, the patient's spasms were still not controlled. On the 12th day of treatment, the patient was started on thiopental 30 mg/hour. At the same time, the patient's administration of MgSO₄, midazolam, and propofol was also stopped.

On the 15th day, the patient began to experience worsening of the condition in the form of autonomic dysfunction. The severity of the patient's disease was measured using the Ablett score, and the patient was included in the severe category because he received a score of 4. Vital signs were examined: blood pressure fluctuated between 70-180/50-90 mmHg, respiratory rate 29 breaths/minute, pulse 70-170 beats/minute, and body temperature 38°C. Apart from that, there was also an increase in sputum production and rales in both lung fields. Routine laboratory examination results showed hemoglobin 8.8 g/dL (13.5-17.5 g/dL), hematocrit 27.1% (41-53 %), albumin 2.6 g/dL (3.4-4.8 g/dL), and calcium 1.97 mmol/L (2.15-2.57 mmol/L), and blood gas analysis results showed pH 7.61 (7.35-7.45), pO₂ 126 mmHg (83-108 mmHg), pCO₂ 33 mmHg (35-45 mmHg), and HCO₃ 33 mmol/L (22-26 mmol/L) which indicates metabolic alkalosis. Chest radiography showed pericardial infiltrates in both lungs (**Figure 1**), and sputum culture showed growth of multidrug-resistant *Pseudomonas aeruginosa* and was only sensitive to ceftazidime, gentamycin, tobramycin, cefepime, amikacin, piperacillin, colistin, and polymyxin B. This condition was corrected by administering two bags of PRC transfusion, 100 ml of 20% albumin, and a 0.1 mcg/kg/minute norepinephrine pump to treat hypotension. The clinical microbiologist eventually recommended intravenous administration of a combination of gentamycin 80 mg three times a day and ceftazidime 1 gram twice daily according to the antibiotic sensitivity test results, each for seven days, and metronidazole was discontinued on day 21.

The following day, the patient's hemodynamic status and metabolic panel gradually improved; simultaneously, the patient's spasms also began to be controlled since being given thiopental. On the 25th day, the patient was declared stable, so all sedative and anti-spasm agents were stopped, except that diazepam was still given orally at 5 mg three times a day. Next, the patient was transferred to a regular inpatient room, and finally, on the 30th day, the tracheostomy was removed, and the patient was discharged for outpatient care.

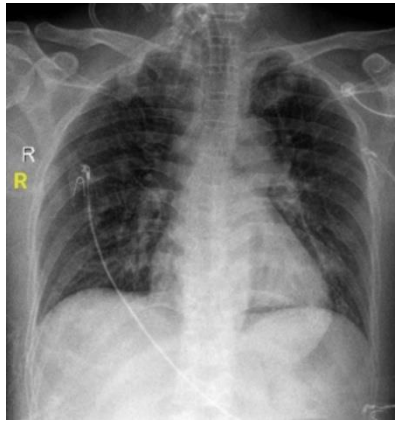


Figure 1. Chest x-ray of the patient that shows pneumonia

Discussion

Tetanus is an infectious disease caused by the neurotoxin, "tetanospasmin," which is produced by the bacterium *Clostridium tetani* and attacks the neuromuscular system and is characterized by muscle spasms and rigidity without impaired consciousness (Dong et al., 2019; Karnad & Gupta, 2021). In 2019, around 73.000 patients worldwide suffered from tetanus, with 27.000 neonatal tetanus infections (Fava et al., 2020). Tetanus is a disease that can be prevented through vaccination, proper wound care, tetanus antitoxin injections after injury, adequate monitoring, and hygienic birth and surgical practices (Bae & Bourget, 2023; Centers for Disease Control and Prevention, 2022). In general, the global incidence of deaths due to tetanus has also decreased by 88% from 1990 to 2019. Although significant progress has been made to reduce the impact of this disease, the burden of tetanus remains high, especially in low-income developing countries, especially in Africa, South Asia, and Southeast Asia, indicating the need for more efforts and interventions in various fields (Lisboa et al., 2011; Sanchez-Grillo et al., 2023).

In general, *C. tetani* can enter the human body through minor wounds or abrasions, especially in anaerobic conditions, such as tissue necrosis, which has low oxidation-reduction potential. Often, the source of tetanus infection is a trivial wound that goes unnoticed, such as a minor laceration caused by a splinter of wood, metal, or thorns (Ergonul et al., 2016). The incubation period (the interval between injury and the onset of symptoms) generally ranges from 3 to 21 days but can sometimes be several weeks. The severity of symptoms depends on the location or distance from the central nervous system, and more severe symptoms are generally associated with a shorter incubation period (Hassel, 2013). In this case, our patient had a history of being pricked by a tree thorn on his right big toe and only experienced symptoms after four days. The incubation time in this patient was four days, which indicates a rapid incubation period compared to the average incubation time of around seven days (Bae & Bourget, 2023). Faster incubation time is related to the severity of the disease, and this is related to the condition of patients who experience severe tetanus. Another aggravating factor is the patient's unknown immunization status (Setiyandari et al., 2023).

Based on the inoculation site and symptom presentation, tetanus can be categorized into four types. First, generalized

tetanus is the type of tetanus with the highest prevalence (around 95%), which begins with symptoms of dysphagia, muscle spasm, and trismus in the head and neck, which then develops into stiffness in all muscle groups and opisthotonus. Spasms are usually triggered by physical stimuli such as noise, bright light, touch, suction, and injection. Second, tetanus is localized and characterized by rigidity limited to the site of spore inoculation. Third, cephalic tetanus is associated with contaminated wounds on the head or chronic otitis media, which can affect the cranial nerves. Fourth, neonatal tetanus usually occurs in newborns under one month old and is related to an umbilical cord infection (Karnad & Gupta, 2021; Li et al., 2023).

Tetanus can also be classified according to severity using the modified Ablett score (**Table 1**). One of the most severe tetanus complication infections is autonomic dysfunction. This condition is usually characterized by episodes of tachycardia and hypertension, sometimes followed by alternating sudden bradycardia and hypotension. Also, symptoms of profuse sweating, increased respiratory secretions, changes in bowel function, and urinary retention are often found. These symptoms are paralleled by a dramatic increase in adrenaline and noradrenaline levels, which can also lead to myocardial necrosis. The mechanism that may underlie autonomic dysfunction in tetanus patients is the effect of tetanus toxin on the brain stem and binding to sympathetic and adrenergic neurons (Karnad & Gupta, 2021; Yen & Thwaites, 2019). In our case, the patient experienced hypotension and tachycardia on the 15th day of treatment after the patient's blood pressure fluctuated wildly from 70-180/50-90 mmHg.

The survival of tetanus patients may improve if they are treated in a high-performance intensive care unit. In the absence of mechanical ventilation, respiratory failure related to laryngeal spasm is known to be the most common cause of death, whereas autonomic dysfunction related to tetanus is the leading cause of death in mechanically ventilated patients (Hassel, 2013; Lisboa et al., 2011). Our patients were managed comprehensively and meticulously with the best available resources during the 30-day hospitalization. Similar to previous case reports, a patient in Saudi Arabia remained for more than 40 days in the ICU after the patient was diagnosed with tetanus (Alfilfil et al., 2015).

Table 1. Ablett Score for Classification of Tetanus Severity (Yen & Thwaites, 2019)

Grade	Symptoms
Grade 1: mild	Mild to moderate trismus, generalized spasticity, no respiratory distress, no spasms, little or no dysphagia
Grade 2: moderate	Moderate trismus, marked rigidity, mild to moderate but short spasms, respiratory rate (>30 breaths/min), mild dysphagia
Grade 3: severe	Severe trismus, generalized spasticity, prolonged spasms, respiratory rate (>40 breaths/min), apneic spells, severe dysphagia, tachycardia (>120 beats/min)
Grade 4: very severe	Clinical features of grade 3 tetanus, plus severe autonomic dysfunction involving the cardiovascular system, severe hypertension and tachycardia alternating with relative hypotension and bradycardia

In another similar case, a 53-year-old woman was diagnosed with tetanus and was treated in the ICU for six weeks (Sanchez-Grillo et al., 2023). This indicates the need to educate patients and their families regarding the possible length of treatment for tetanus.

In this patient, Tetagam® was started with a dose of 3000 IU as initial management of tetanus (recommended dose: 3000-6000 IU). Tetagam® is HTIG, which is given as a precaution to at-risk patients because the patient experienced a wound on his left big toe after being exposed to a tree thorn. Unknown immunization status also causes patients to be given HTIG. Human tetanus immunoglobulin works by neutralizing the tetanospasmin toxin that has not yet bound to the central nervous system, so it is hoped that it can reduce the severity of the disease (Bae & Bourget, 2023; Fava et al., 2020).

Management of spasms and autonomic instability is also a priority in treating tetanus. Traditionally, benzodiazepine agents, such as diazepam and midazolam, have been used to control muscle spasms due to their availability even in resource-limited settings and their ability to exert muscle relaxant, anticonvulsant, sedative, and anxiolytic effects. However, in some cases, such as ours, the use of a combination agent of benzodiazepine, morphine, propofol, and thiopental may be considered to control refractory spasms (Karnad & Gupta, 2021; Lisboa et al., 2011). In tetanus, MgSO₄ has also been widely used because it has been proven to reduce spasms, cause vasodilation, control hypertension, reduce heart rate, reduce systemic catecholamine levels, and reduce autonomic fluctuations (Hassel, 2013). Magnesium sulfate is given intravenously as a 5-gram bolus followed by continuous infusion at 2-3 grams/hour until spasm is controlled (Bae & Bourget, 2023; Rodrigo et al., 2014).

In addition, tetanus patients are also susceptible to complications such as pneumonia due to the need for long-term mechanical ventilation. In this case, the patient's pneumonia was caused by *Pseudomonas aeruginosa*, which is generally closely related to multidrug resistance. According to the culture and resistance testing results, the patient was successfully treated with antibiotics intravenously for seven days, including gentamycin 80 mg three times a day and ceftazidime 1 gram twice a day.

Management of respiratory status, cardiovascular complications, and autonomic dysfunction is critical for the survival of tetanus patients. This case report highlights the need for care of tetanus patients in the ICU, the importance of multidisciplinary collaboration, drug selection tailored to the patient's condition, and appropriate management of

complications. In addition, health services must focus on providing regular booster vaccines to the general public to prevent tetanus (Alhawal et al., 2021; Dong et al., 2019). The main limitation of writing this case report is the lack of external validity, so all the procedures we give to patients may not necessarily apply to other patients. In addition, in this case, we also did not perform blood cultures, and we cannot exclude the possibility of overlap between septic shock and autonomic dysfunction, which was the cause of the patient's hypotension.

Conclusion

Tetanus is an infectious disease with a high mortality rate and is still a problem, especially in developing countries. Tetanus can cause autonomic dysfunction, which risks causing respiratory failure and even life-threatening cardiac arrest. Complications such as pneumonia are also tricky and can increase the duration of treatment for tetanus patients. Immediate diagnosis, management of complications, and appropriate treatment play an important role in determining the success of therapy in tetanus patients.

Conflict of interest

The author declares that there is no conflict of interest.

Acknowledgments

We thank the Faculty of Medicine, University of Jember and dr. Soebandi Regional Hospital, Jember, for facilitating the writing of this case report.

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