SUCCESSFUL THERAPEUTIC PLASMA EXCHANGE THERAPY IN SEVERE TETANUS

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ABSTRACT

Introduction: Tetanus is an acute toxemia condition caused by the neurotoxin produced by Clostridium tetani, manifested by periodic muscular spasms. Manifestation could range from localized tetanus to generalized tetanus and cephalic tetanus. Severe forms of tetanus complicate management and mostly result in death because of asphyxia and hyperactivity of the sympathetic system. Therapeutic plasma exchange (TPE), in which plasma is separated from whole blood and replaced with normal saline, albumin, or fresh frozen plasma, could improve survival in toxemia, although studies on TPE for the treatment of tetanus are still lacking.

Case Illustration: A man in his 60s presented to the ER with a complaint of generalized stiffness in his belly, legs, arms, and jaw, for which the patient could hardly open his mouth. The patient was diagnosed with tetanus due to a history of an unhealed wound on the patient's left pinky toe two weeks prior. Patient's condition worsened during the period of admission, requiring intensive care and mechanical ventilation on the fifth day after admission. Two TPE therapies were administered on the fifth and eighth days of admission, with improvement in the patient's clinical condition after 2 days of the second TPE therapy.

Discussion: Indication of TPE has expanded, and severe tetanus could be indicated as one of the TPE indications in line with the principles of management of tetanus to prevent the spread and toxicity of neurotoxins. The general principle of TPE is to remove a circulating molecule from the blood in the hope of improving the patient's clinical condition.

Conclusion: Tetanus is a common case in developing countries, related to a high mortality rate. Management of severe tetanus could be tricky in several cases. Therapeutic plasma exchange (TPE) may be a better therapeutic alternative, with some successful use reported in the treatment of neurological cases.

Keywords: Severe tetanus; Therapeutic plasma exchange

INTRODUCTION

Tetanus is an acute toxemia condition caused by neurotoxin produced by *Clostridium tetani*.[1] Manifested as periodic muscular spasm, tetanus is still a problem, especially in developing countries, with a global incidence of around 1.000.000 cases yearly and an estimated incidence of 0,2/100.000 populations in Indonesia.[2,3] Tetanus is a preventable disease by means of immunization, especially in children, pregnant mothers, as well as hygienic and adequate wound care. But because this is an intoxication and not an infection, tetanus is not transmissible, and vaccination does not include the "herd" effect.[4] Tetanus, including neonatal tetanus, is still a growing problem in developing countries due to inadequate knowledge about tetanus and a lack of coverage of tetanus toxoid (TT) vaccine.[5]

Manifestation could range from localized tetanus to generalized tetanus and cephalic tetanus. Although protocols and pharmacological interventions have limited the mortality and morbidity of tetanus, severe forms of tetanus complicate management and mostly result in death because of asphyxia and hyperactivity of the sympathetic system.[4] Management of tetanus involves preventing further toxin release, neutralizing toxins, and reducing their toxicity.[4,6] Therapeutic plasma exchange (TPE) is one of the models of therapy in which plasma is separated from whole blood and replaced with normal saline, albumin, or fresh frozen plasma. Plasma exchange can improve survival in toxic conditions by removing harmful substances and replacing deficient blood components, but studies on the use of TPE in the treatment of tetanus are still lacking.[7,8] In this case report, we reported a successful case of therapeutic plasma exchange (TPE) in a case of acute toxemia condition of severe tetanus.

CASE PRESENTATION

A man in his 60s presented to our Emergency Department unit with chief complaint of generalized stifin the belly, legs, arms, and jaw, for which the patient couldatient hardly open his mouth. Patient was a farmer with no history of diabetes, hypertension or other chronic ilnesses. There was no history of seizure nor prior sign of fever, acute respiratory tract infection, allergy or other significant medical history. Two weeks prior, the patient's left pinky toe got stuck on a motorcycle kickstand, resulting in an open wound that was cleaned and stitched up at a local clinic. No injection or vaccination was given at that time. One week later, the wound was still not healed with oozing, pus, and pain, especially with movement. Examination of the left fifth toe revealed a 2x1 cm grade II ulcer with pus, surrounding erythema, and edema. The patient's vital signs were normal. On physical examination, abdominal wall rigidity was found in all parts of the abdomen, and the patient's jaw was stiff; he could only open his mouth by two fingerwidths. Neurological examination was normal and no other abnormalities was found. Routine blood examination, electrocardiography, chest x-ray and blood gas analysis showed no sign of abnormalities.

Figure 1. Wound on patient's left pinky toe

On suspicion of tetanus, scoring was done using the Ablett score (Grade II) and the tetanus severity score (7, low risk). Patient was then admitted to the tetanus isolation ward with minimal light, minimal touch, and minimal noise. Intralesional (500 IU) and intramuscular gluteal injection of human tetanus immunoglobulin (Tetagram®)

(2500 IU) were given as well as diazepam via syringe pump (1.5cc/hour), intravenous metronidazole, intravenous metamizole, and throughout debridement of the wound. Patient's condition deteriorated over the next four days with complaints of worsening stiffness and difficulties in mouth opening. Wound culture was performed with ceftriaxone, the suggested antibiotic, which was started on the fifth day of admission. Blood gas analysis showed partially compensated metabolic alkalosis. Patient then moved into the intensive care unit, requiring mechanical ventilation and planned to undergo therapeutic plasma exchange therapy two times on the fifth and eighth days of admission.

Two days after the second therapeutic plasma exchange therapy, the patient's condition got better, and he started to be able to open his mouth one fingerwidth wide. The patient's condition continued to improve, and he was discharged after 18 days of admission. One week after discharge, the patient was able to start walking with assistance and could eat and drink normally.

DISCUSSION

Tetanus

Tetanus is an acute toxemia condition caused by bacteria *Clostridium tetani, a spore-producing bacterium found on soil and decomposi*tion of organic matter. *Clostridium tetani* spores can survive for months and even years before entering the host through an infected wound and releasing the tetanus neurotoxin (TeNT). There were two kinds of TeNT produced, tetanolysin and tetanospasmin. Tetanolysin, a hemolysin, had questionable clinical importance because this toxin is inhibited by oxygen and serum cholesterol.[9,10] On the other hand, tetanospasmin mostly contributed to the clinical manifestation of tetanus that spread from the infected wound by hematogenous and lymphatic spread before reaching motor neurons. Tetanospasmin is degraded, internalized in endosome vesicles, and transported by means of retrograde axonal transport to presynaptic nerve mediated by the SNARE protein. These toxins then inhibit the release of glycine and gamma-aminobutyric acid (GABA), preventing the inhibition of motor neurons that manifests as neuroparalytic syndromes such as spastic paralysis and stiffness.[4,11]

The incubation period of tetanus ranged from 3 to 36 days, with a mean period of 12 days. Manifestation of tetanus is classified into local tetanus, generalized tetanus, tetanus neonatorum, and cephalic tetanus.[1,4] Localized tetanus commonly manifests as rigidity and spasm on contaminated limb extremities that will evolve into generalized tetanus in 2/3 of cases. Generalized is the most common form, begins with stiffness of the jaws (trismus, lock-jaw), contracture of facial and neck muscles (opisthotonos), rigidity of abdominal and erector spinal muscles, then evolved into pharyngeal and laryngeal spasms with dysphagia. Spasmodic contraction of respiratory muscless causes asphyxia, the most common cause of death in tetanus. Late autonomous manifestation may develop because of overactivity of sympathetic neurons as a result of inhibition of neurotransmitter release from inhibitory neurons of the spinal cord.[1,6]

The severity of tetanus is determined by the location of the wound, the size of the wound, the extent of necrotic area, and the number of spores contaminating the wound. Scoring systems such as the Ablett score and the tetanus severity score could predict the severity and prognosis of suspected tetanus conditions.[1] Main management of tetanus involves preventing further toxin release, neutralizing toxins, and reducing their toxicity. The debridement of the wound and administration of antibiotics could prevent further production and release of toxins. Toxins can be neutralized with tetanus antitoxin (TAT) and equine/human tetanus immunoglobulin (HTIG). Toxicity affecting the respiratory system may bring the need for mechanical ventilation and continuous renal replacement therapy (CRRT) [4,10].

Therapeutic Plasma Exchange

American Society for Apheresis (ASFA) 2019 guidelines defined therapeutic plasma exchange (TPE) as "A therapeutic procedure in which the blood of the patient is passed through a medical device which separates plasma from the other components of bloo". TPE involves removal of plasma and replacement with a solution either a colloid solution, a combination of a crystalloid/colloid solution, or fresh frozen plasma (FFE).[8,12] Initially, as a treatment for hematological diseases, TPE has been indicated for a variety of pathologies, including kidney, autoimmune, and

neurological diseases, and gained popularity in the recent Coronavirus disease-19 (COVID-19) pandemic.[7,13] Neurological diseases previously treated by TPE including myasthenia gravis, Guillain-Barré syndrome, neuromyelitis optica spectrum disorder, chronic inflammatory demyelinating polyneuropathy and autoimmune encephalitis. Case reports and small observational studies also report the use of TPE in treatment of septicemia or meningococcemia.[12,14] AFSA classified the indication of TPE therapy in several category, (1) Category I represents diseases for which TPE is a first-line treatment (e.g., Guillain-Barré syndrome [GBS]); (2) Category II includes pathologies for which TPE is accepted as second-line (e.g., acute disseminated en- cephalomyelitis after steroid failure) therapy; (3) Category III are indications that are not established and are considered on a case-by-case basis (e.g., IgA nephropathy); (4) Category IV are the indications where the literature has proven no benefit or has shown deleterious effects. [7]

The evolution in understanding the molecular mechanisms underlying several pathologies has expanded the indications for therapeutic plasma exchange (TPE).[7] Severe tetanus could be indicated as one of TPE indications inline with principle of management of tetanus to prevent the spread and toxicity of neurotoxins. The general principle of TPE is to remove a circulating molecule from the blood in the hope of improving the patient's clinical condition. Although several cases of neurological conditions related to inflammatory and infectious mechanisms have already been successfully treated with TPE, TPE also has the potential to cause harm by diluting or attenuating the host's adaptive response to infection.[14] Complications of TPE include electrolyte disturbances, coagulopathy due to depletion, access-associated complications, and reactions to FFP (anaphylaxis, rigors, and hypotension).[7,8]

In this case report, we report a man in his mid-40s with severe tetanus that worsened during the period of admission, requiring intensive care and mechanical ventilation on the fifth day after admission. Two TPE therapies on the fifth and eighth days of admission, then given with improvement of the patient's clinical condition after two days of the second TPE therapy, until the patient was discharged after a good clinical evaluation on the eighteenth day of admission. We successfully performed therapeutic plasma exchange (TPE) in a case of severe tetanus, and further studies on this method are needed to improve the management of tetanus cases in the future.

CONCLUSION

Tetanus is common in developing countries and is associated with a high mortality rate. Management of severe tetanus could be tricky in several case. Therapeutic plasma exchange (TPE) may be a better therapeutic alternative, with some successful use reported in the treatment of neurological cases.

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Author Contributions

Conceptualization, P.N.; methodology, P.N. and Y.M.P.; validation, R.S.B.S. and A.; formal analysis, M.S.K.; investigation, R.P.Y. and H.S.U.; resources, A.; data curation, P.N.; writing—original draft preparation, P.N.; writing—review and editing, R.S.B.S. and A.; visualization, Y.M.P.; supervision, A.; project administration, H.S.U. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy regarding the patient's identity.

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Informed Consent Statement

Informed consent was obtained from the patient involved in the study to publish this paper.

Conflicts of Interest

The authors declare no conflict of interest.

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