Iliopsoas hematoma as a complication of tetanus

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Introduction
Tetanus is a neurological disease caused by the tetanus toxin of Clostridium tetani, which inactivates inhibitory neurotransmission of motor and autonomic neurons in the spinal cord and brainstem. Increased muscle tone leads to neck stiffness, trismus, risus sardonicus, dysphagia, and opisthotonus. Episodic muscle spasms that are strong enough to cause bone fractures induce severe pain and respiratory failure; approximately half of patients require intubation and mechanical ventilation. Moreover, overactivation of the autonomic nervous system causes tachycardia, arrhythmias, and labile blood pressure.

The basis of tetanus treatment involves neutralization of unbound toxin, removal of source of infection, control of spasticity, and management of autonomic dysfunction. Because long-term sedation is often required to control muscle tone and spasticity, additional supportive intensive care treatments are also necessary, including airway management and prophylaxis of ventilator-associated pneumonia, decubitus ulcers, gastrointestinal hemorrhage, and thromboembolism.

Iliopsoas hematoma is a rare but serious bleeding event that occurs in patients with hemophilia, those who have undergone trauma, and those who are receiving anticoagulation therapy. The incidence and mortality of iliopsoas hematoma as a complication of anticoagulant therapy are 0.6–6.6% and 20%, respectively. In terms of complications of tetanus, there has been one report of a case of rectus abdominis sheath hematoma; however, no cases of iliopsoas hematoma have been reported to date. Common symptoms and signs of iliopsoas hematoma include abdominal pain, hip and upper thigh pain, hypotension, anemia, and back pain. Detection of iliopsoas hematoma during tetanus management may sometimes be difficult because pain symptoms are difficult to detect when the patient is receiving sedation therapy; furthermore, based on general signs such as hypotension and tachycardia, patients may be misdiagnosed with tetanus-associated dysautonomia.

Due to lack of previous reports of clinical data, characteristics of iliopsoas hematoma arising during tetanus management remain unclear. Hence, in this case series, we sought to evaluate the incidence of iliopsoas hematoma in tetanus; we also aimed to describe the clinical courses of patients with iliopsoas hematoma, with the goal of identifying clinical factors that could aid in its detection.

Materials and Methods
This was a retrospective case series study.

Study population. Twenty-one consecutive patients with a clinical diagnosis of tetanus who were hospitalized and treated at the Department of Neurology in University of Miyazaki Hospital, Japan, from April 2004 to March 2017...
were enrolled in this study. The study protocol was approved by the Ethics Committee of the University of Miyazaki, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects or their family members.

We evaluated age, sex, severity of tetanus, laboratory data, treatment, and complications of patients with or without iliopsoas hematoma. Disease severity was evaluated on admission according to the Ablett classification of tetanus severity\(^1\): Grade 1 (mild), mild trismus and no respiratory compromise; Grade 2 (moderate), moderate trismus and respiratory embarrassment; Grade 3 (severe), severe trismus and respiratory involvement; and Grade 4 (very severe), Grade 3 disease with severe autonomic disturbances. We also assessed disease severity according to the modified Rankin scale\(^1\) on discharge. Progressive anemia was defined as more than a 25% reduction in hemoglobin level per week. To prevent muscle spasms, all patients were treated with \(\gamma\)-aminobutyric acid-ergic (GABAergic) medications, including diazepam, propofol, and baclofen. Depending on disease severity, some patients were intubated or underwent tracheostomy and received rocuronium and magnesium.

**Diagnosis of iliopsoas hematoma.** Patients were diagnosed with iliopsoas hematoma based on results of abdominal computed tomography (CT). All patients underwent abdominal CT at least once during their hospitalization. Patients with iliopsoas hematoma were subjected to CT to detect progressive anemia whereas patients without hematoma were subjected to CT to examine other organs.

**Results**

**Characteristics of tetanus patients.** Patient characteristics are summarized in Table 1. Four of 21 patients (19%) developed iliopsoas hematoma during the clinical course of tetanus. Of 15 patients who received anticoagulation therapy, four (27%) developed iliopsoas hematoma; that is, all patients with iliopsoas hematoma were receiving anticoagulation therapy. Clinical summary, laboratory data, and abdominal CT results of these four patients are provided in Table 2 and Figure 1. Detailed clinical courses are described below.

**Case series.** Case 1. A 71-year-old woman with no notable medical history was admitted owing to progressive dysphagia and severe neck rigidity for the past two weeks. On admission, she had trismus and developed episodic muscle spasms in the entire body, leading to a diagnosis of Grade 3 tetanus. She was started on symptomatic treatment with ventilator management for respiratory insufficiency; she received midazolam for muscle spasms, opioid for pain, and UFH for VTE. Her symptoms improved with time;

### Table 1 Demographics and clinical characteristics of the patients

| Demographics                          | Total (\(N = 21\)) | Iliopsoas hematoma | Case 1 | Case 2 | Case 3 | Case 4 |
|---------------------------------------|---------------------|--------------------|--------|--------|--------|--------|
| **Demographics**                      |                     |                    |        |        |        |        |
| Age                                   | 71 (61–81)          | 76                 | 71     | 76     | 81     | 85     |
| Men                                   | 13 (61.9)           | 1                  | F      | F      | F      | M      |
| BMI (kg/m\(^2\))                      | 21.6 (19.3–23.7)    | 22.6               | 21.5   | 25.5   | 19.3   | 23.7   |
| Past medical history                  |                     |                    |        |        |        |        |
| Hypertension                          | 8 (38.1)            | 3                  | N      | Y      | Y      | Y      |
| Diabetes mellitus                     | 2 (9.5)             | 0                  | N      | N      | N      | N      |
| Smoking history                       | 7 (33.3)            | 0                  | N      | N      | N      | N      |
| Heavy alcohol history                 | 6 (28.6)            | 0                  | N      | N      | N      | N      |
| History of traumatic injuries         | 10 (47.6)           | 1                  | N      | Y      | N      | N      |
| **Disease severity**                  |                     |                    |        |        |        |        |
| Tetanus staging                       | 3 (2–4)             | 2.5                | 3      | 2      | 2      | 3      |
| mRS on discharge                      | 3 (1–4)             | 4                  | 5      | 4      | 3      | 4      |
| **Treatment/Procedure**               |                     |                    |        |        |        |        |
| Anticoagulation therapy               | 15 (71.4)           | 4                  | Y      | Y      | Y      | Y      |
| Neuromuscular blockade                | 7 (33.3)            | 0                  | N      | N      | N      | N      |
| **Complications**                     |                     |                    |        |        |        |        |
| Progressive anemia                    | 6 (28.6)            | 4                  | Y      | Y      | Y      | Y      |
| RBC transfusion                       | 2 (9.5)             | 2                  | N      | N      | Y      | Y      |
| Dysautonomia                          | 5 (23.8)            | 0                  | N      | N      | N      | N      |
| Sepsis                                | 9 (42.9)            | 1                  | N      | N      | N      | Y      |
| Death                                 | 1 (4.8)             | 0                  | N      | N      | N      | N      |

Categorical variables are shown as numbers (percentages), and continuous variables are shown as medians (25th–75th percentiles). BMI, body mass index; M, males; N, no; F, females; mRS, modified Rankin Scale; RBC, red blood cell; Y, yes.
however, despite receiving anticoagulation therapy, her anemia progressively worsened, and her D-dimer level did not decrease (Fig. 1a). On day 19 after admission, bilateral iliopsoas hematoma was detected by abdominal CT (Fig. 1b). Her hemoglobin level gradually returned to normal after UFH infusion was discontinued. She was discharged 25 days after admission.

**Case 2.** A 67-year-old woman with nail injuries caused while hammering was admitted owing to progressive dysphagia and limited mouth opening, which led to difficulty in eating and drinking. She was diagnosed with Grade 2 tetanus; she received midazolam, opioid, and UFH along with ventilator management. Her symptoms improved gradually; however, her anemia progressed, and her D-dimer levels did not decrease (Fig. 1c). On day 22 after admission, bilateral iliopsoas hematoma was detected by abdominal CT, after which UFH administration was discontinued (Fig. 1d). She was discharged 45 days after admission.

**Case 3.** An 81-year-old woman with hypertension was admitted owing to progressive neck pain, dysphagia, and limited mouth opening for the past one week. She was diagnosed with Grade 2 tetanus; she received midazolam, magnesium sulfate, opioid, and UFH along with ventilator management. Her hemoglobin level decreased progressively following admission, resulting in discontinuation of UFH 14 days after admission. Along with progressive anemia, her D-dimer levels increased gradually (Fig. 1e). On day 22, right iliopsoas hematoma was detected by abdominal CT (Fig. 1f); she was discharged on day 49.

**Case 4.** An 85-year-old man with hypertension was admitted owing to progressive dysphagia, neck pain, limited mouth opening, and muscle spasms in the entire body. He was diagnosed with Grade 3 tetanus and required mechanical ventilation; he received midazolam, dexmedetomidine, opioid, and UFH. Progressive anemia and increased D-dimer levels were observed after administration, resulting in discontinuation of UFH seven days after admission (Fig. 1g). On day 8, bilateral iliopsoas hematoma was detected by abdominal CT (Fig. 1h). Although he developed sepsis during hospitalization, he was discharged on day 74.

All four patients with iliopsoas hematoma received anticoagulants and their activated partial thromboplastin time values were less than 200% of baseline values when their hemoglobin levels were at the lowest point during the clinical course (Table 2). Accompanied by progressive anemia, D-dimer levels increased or did not decrease despite anticoagulation therapy (Fig. 1). UFH administration was discontinued after detection of iliopsoas hematoma or just before

| Patients | Hemoglobin (g/dL) | Platelet (10^3/µL) | PT-INR | APTT (seconds) | D-dimer (µg/mL) |
|----------|------------------|-------------------|--------|---------------|-----------------|
| Case 1   | 12.6             | 407               | 1.22   | 43.2          | 7.65            |
| Case 2   | 13.0             | 458               | 1.28   | 50.5          | 5.24            |
| Case 3   | 11.3             | 429               | 1.15   | 29.0          | 7.25            |
| Case 4   | 9.9              | 245               | 1.32   | 41.9          | 13.03           |

APTT, activated partial thromboplastin time; PT-INR, prothrombin time international normalized ratio.

Figure 1 Clinical courses (left column) and abdominal computed tomography (CT) scans (right column) of the four patients who developed iliopsoas hematoma during tetanus treatment. All patients received unfractionated heparin intravenously for venous thromboembolism. Despite anticoagulation therapy, D-dimer levels increased or did not decrease and anemia progressed throughout the clinical course in all four patients. Each asterisk indicates the day on which abdominal CT was performed (Patient 1, 8th day after admission; Patient 2, 19th day after admission; Patient 3, 22nd day after admission; Patient 4, 22nd day after admission). Arrowheads indicate iliopsoas hematomas in abdominal CT scans.
Observation of iliopsoas hematoma in tetanus

In this study, we observed the following: (i) 19% of the all patients.14 Many tetanus patients have VTE-related risks medical patients is recommended for only high-risk coagulation therapy for VTE should be considered carefully. and 12.9%, respectively.13 Therefore, an indication of anti-VTE and pulmonary embolism for one year were 9.2% and 12.9%, respectively.13 There, an indication of anticoagulation therapy for VTE should be considered carefully. Generally, VTE prophylaxis in acutely ill hospitalized medical patients is recommended for only high-risk patients.14 Many tetanus patients have VTE-related risks such as critical illness, systemic infection, immobility, and elevated D-dimer levels, which classify the patients as high risk. Meanwhile, it has been estimated that tetanus patients have a low risk of major bleeding on receiving anticoagulation therapy for VTE,15 owing to the absence of coagulopathy, active bleeding, or renal or liver dysfunction. Considering the high incidence of iliopsoas hematoma in tetanus, the bleeding risk in tetanus may have been underestimated; tetanus itself might be a bleeding risk factor.

Iliopsoas hematoma, which has been reported in patients with traumatic or non-traumatic conditions, is commonly seen in patients receiving anticoagulation therapy, patients with bleeding abnormalities, and patients undergoing hemodialysis; it is the most frequent intramuscular hemorrhage in anticoagulation-related conditions.16 In mechanistic terms, forceful muscular strain, diffuse small-vessel atherosclerosis, or unrecognized minor trauma may result in iliopsoas hematoma.7 However, due to lack of previous studies, it remained unclear why a high incidence of iliopsoas hematoma was observed during tetanus management.

We speculated that the following mechanism might be responsible for the high incidence of iliopsoas hematoma during tetanus management. Tetanus causes hypercontraction of the proximal and truncal muscles; tetanic muscle spasms might occur in the truncal muscles even when patients appeared to be fully relaxed due to sedation. Thus, muscular injury induced by muscular spasms might be the underlying cause of iliopsoas hematoma in tetanus patients.

According to the clinical courses of the four patients with iliopsoas hematoma, only progressive anemia and the trend in D-dimer level hinted at bleeding. Because all patients were under sedation and analgesia, we could not detect subjective symptoms of hematoma such as hip and upper thigh pain. Moreover, in critically ill patients, anemia is caused by several conditions other than bleeding, including inflammation, adverse effects of medication, or phlebotomy.17 Thus, both hemoglobin and D-dimer levels, which are also useful for evaluating various bleeding conditions,18,19 should be regularly monitored in patients with tetanus. Progressive anemia with increased D-dimer levels may prompt consideration of iliopsoas hematoma as a differential diagnosis; this is important because high mortality is observed in patients with iliopsoas hematoma (17% in all patients and 20% in patients receiving anticoagulation).8 In our four patients, cessation of anticoagulation therapy prevented worsening of their prognosis.

To our knowledge, this is the first case series that describes iliopsoas hematoma in tetanus. The incidence of tetanus-related iliopsoas hematoma was higher than that of anticoagulation-related iliopsoas hematoma. However, our sample size was small, and the results should be confirmed using large-scale studies. Progressive anemia and increased D-dimer levels may be indicators of iliopsoas hematoma in patients with tetanus who are receiving anticoagulation therapy. Clinicians should carefully consider the indication of VTE prophylaxis in patients with tetanus and pay attention to the trend in hemoglobin and D-dimer levels during tetanus management.

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