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Hyperpyrexic Toxic Shock Syndrome in Association with TSST-1 Cross-Reactive Superantigen SE-like X-Producing *Staphylococcus aureus*: Case Report, Toxin Analysis and a Proposed Case Definition

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Abstract: Herein, we report two additional cases of extreme pyrexia and rapid death due to *Staphylococcus aureus* infection. The organisms produced a variant superantigen, cross-reactive with toxic shock syndrome toxin-1 (TSST-1 cross-reactive superantigen SE-like X), which we purport to be the causative agent for this syndrome.

Keywords: toxic shock syndrome; hyperpyrexia; *Staphylococcus aureus*; staphylococcal superantigen; TSST-1

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Introduction

Hyperthermia, as opposed to fever, is a failure of the thermoregulatory system. Temperatures exceeding 41 °C (105.8 °F) are characteristic of clinical diagnoses that represent a failure of thermoregulation, such as malignant hyperthermia or neuroleptic malignant syndrome. Severe bacterial infections, such as staphylococcal toxic shock syndrome, can produce relatively high fevers but rarely produce temperatures exceeding 41.7 °C (107 °F).

We report one confirmed and one probable case of hyperpyrexic toxic shock syndrome (HTSS), adding to the two cases previously described [1]. All four patients experienced an inexorable rise in temperature to ≥42.2 °C (≥108 °F) associated with hypotension and subsequent cardiovascular collapse and death. In three cases, *Staphylococcus aureus (S. aureus)* that produced TSST-1 cross-reactive superantigen SE-like X was isolated.

Materials and Methods

S. aureus was isolated by culture on blood agar plates, and organisms were identified as catalase and coagulase-positive, Gram-positive cocci.

The ability of the organisms to produce pyrogenic toxin superantigens (SAgs), including staphylococcal enterotoxins A, B, C, D, E, and G; superantigen-like pyrogenic toxins (SE*l*s) I, K, L, M, N, O, P, Q, U, and X; and toxic shock syndrome toxin-1 (TSST-1), was determined by PCR [2]. All organisms were positive for cytotoxins based on hemolysis of both sheep and rabbit red blood cells. Methicillin resistance was determined by culture in the presence of oxacillin.

Case Reports

Patient 1 was a 57-year-old obese male who presented to the emergency department for confusion and cyanosis with initial oxygen saturations of 70–80%. After stabilization, he denied any significant past medical history, drug allergies, or chronic prescription medication use. He was diagnosed with COVID-19 infection two weeks prior. Upon examination, his temperature was 36.8 °C (98.2 °F), heart rate 122 beats per minute, respirations 28 per minute, blood pressure 128/89 mm Hg, and oxygen saturations 91% on a non-rebreather mask at 25 liters per minute with 100% fraction of inspired oxygen (FiO_2). His physical exam was remarkable for dyspnea and bilaterally diminished breath sounds. His white blood cell count was 10.4 × 10^3/µL, with 89% neutrophils and 8% lymphocytes, hemoglobin 17.0 gm/dL, and platelets 358,000/µL. Electrolytes revealed a blood urea nitrogen (BUN) of 93 mg/dL and creatinine of 4.88 mg/dL. Liver function tests (LFTs) showed an aspartate aminotransferase (AST) of 107 units/L. The C-reactive protein (CRP) was 173 mg/L, lactate dehydrogenase (LDH) 691 units/L, ferritin 5,41 mg/mL, lactic acid 3.3 mmol/L, D-dimers 1.94 mg/L and brain natriuretic peptide (BNP) 23 pg/mL. Rapid testing for Influenzas A and B was negative, while his SARS-CoV-2 rapid antigen test was positive. Chest X-rays showed mild cardiomegaly and diffuse bilateral infiltrates. He was admitted to the intensive care unit (ICU) on bilevel positive airway pressure (BiPAP), given tocilizumab, and started on dexamethasone, ceftriaxone, and azithromycin. At the time of ICU admission, his creatine kinase (CK) was 225 U/L. On hospital day 4, he became confused and agitated, requiring intubation and mechanical ventilation with 90% FiO_2. The creatinine declined to 2.89 mg/dL, and the white blood cell (WBC) count was 11.3 × 10^3/µL. Blood cultures remained negative. On hospital day 7, he remained mechanically ventilated with a FiO_2 of 80%. His WBC count rose to 13.6 × 10^3/µL, creatinine remained elevated at 3.22 mg/dL, CRP decreased to 9.1 mg/L, and ferritin stayed elevated at 4.599 mg/mL. Tapering of steroids was initiated. On hospital day 8, he became febrile with temperatures as high as 39.9 °C (103.8 °F) measured orally. Blood, urine, and sputum cultures were obtained, and piperacillin/tazobactam and vancomycin were initiated. From 16:00 on hospital day 8 to 02:00 on hospital day 9, his temperature steadily rose from 38.1 °C (100.6 °F) to 42.4 °C (108.3 °F), which was the last recorded orally measured temperature. During this time, he became increasingly hypotensive, requiring blood pressure support. At approximately 4:00 on hospital day 9, he suffered a cardiac arrest and could not be resuscitated. The following day, moderate growth of methicillin-resistant *S. aureus* (MRSA) was reported on the sputum culture.

Patient 2 was a 33-year-old male group home resident presenting to the emergency department with complaints of heavy breathing. His past medical history included trisomy 21, gastroesophageal reflux, hypothyroidism, unspecified mood disorder, and moderate intellectual delay. Chronic medications included quetiapine, clomipramine, and topiramate. His temperature was 36.3 °C (97.3 °F), heart rate 106 beats per minute, respirations 46 per minute, blood pressure 122/64 mm Hg, and oxygen saturations 88% on room air, which improved to 93% on 2 liters of oxygen per minute via nasal cannula. He appeared anxious and tachypneic but was alert, oriented, and able to answer simple questions consistent with his baseline. His WBC count was 12.4 × 10^3/µL with 92% neutrophils, hemoglobin 13.1 gm/dL, and platelets 217,000/µL. Renal function was normal. Liver function tests revealed an AST of 144 IU/L, alanine aminotransferase (ALT) of 301 IU/L, alkaline phosphatase of 196 IU/L, and total bilirubin of 1.9 µm/L. Rapid antigen testing for Influenzas A and B and SARS-CoV-2 were negative. Chest X-rays revealed a right basilar infiltrate. Computed tomography angiogram showed a right lower lobe consolidation with no evidence of pulmonary embolus. *Legionella pneumophila* and *Streptococcus pneumoniae* urine antigen tests were negative. Ceftriaxone and azithromycin were initiated, and he was admitted to the hospital with a diagnosis of right lower lobe pneumonia. On hospital day 3, his WBC count rose to 15.9 × 10^3/µL, and his oxygen saturations dropped, requiring temporary application of BiPAP. Ceftriaxone was discontinued, and piperacillin/tazobactam was initiated. On

hospital day 4, the WBC count rose to 17.4 × 10^3/µL. However, the patient clinically improved while on only 2 liters per minute of oxygen by nasal cannula. On hospital day 5, the white blood cell count dropped to 13 × 10^3/µL, and the chest X-ray showed some improvement. However, the patient experienced another episode of respiratory distress overnight, again requiring a temporary application of BiPAP. From the night of hospital day 5 into the morning of hospital day 6, the patient experienced respiratory distress with oxygen saturations less than 90% on 100% FiO_2 via BiPAP, and his temperature rose to 40.4 °C (104.7 °F), at which point he was transferred to the ICU. His WBC was 17.3 × 10^3/µL, and intravenous vancomycin was added. After ICU transfer, he required intubation and had an axillary temperature of 41.8 °C (107.2 °F). The diagnosis of neuroleptic malignant syndrome was entertained, and dantrolene and bromocriptine were ordered. His CK was 1.206 IU/L, and at this point, cooling measures, including iced fluid infusion and ice water irrigation via foley catheter and oro-gastric tube, were initiated. Despite cooling efforts, his temperature continued rising, peaking at 42.8 °C (109 °F), eventually leading to subsequent cardiac arrest and death.

Discussion

From a laboratory perspective, the *S. aureus* isolates from HTSS patients all produced SAgs, notably staphylococcal enterotoxin-like X (SE*l*-X). Pyrogenic toxin SAgs are the most potent pyrogens currently known [3]. Like TSST-1, this is a small staphylococcal SAg previously associated with severe staphylococcal pneumonia [4,5].

Similar to TSST-1, SE*l*-X is a group I Sag [5], meaning it has only the standard properties of superantigenicity and is only related immunologically to TSST-1 but not to other SAgs [6]. Both SE*l*-X and TSST-1 have an enhanced ability to cross human barriers to infection compared to other SAgs, which possibly includes the blood–brain barrier [7]. Another previously reported SAg, streptococcal pyrogenic exotoxin C, which is also a close relative to TSST-1, can cross the blood-brain barrier. This ability can lead to fever production through direct stimulation of the hypothalamic fever response control center [8]. Its small size enhances barrier transport and direct stimulation of the hypothalamus, which may account for the association of SE*l*-X with HTSS.

Interestingly, all *S. aureus* isolates produce either SE*l*-X or TSST-1, but rarely both; the reason for this apparent exclusion is unknown [9,10]. However, it is not unusual to find one SAg type associated with human diseases, such as SE*l*-X with HTSS. For example, menstrual TSS, lethal post-influenza TSS, bullous pemphigoid, and eczema herpeticum are highly associated with TSST-1 [5,11–13]. In contrast, both cystic fibrosis and atopic dermatitis isolates of *S. aureus* are enriched for the enterotoxin gene cluster of six SAgs [10,14].

There are now four reported cases of extreme hyperpyrexia and rapid death, three of which occurred in association with the TSST-1 cross-reactive superantigen SE-like X-producing *S. aureus.* The syndrome appears to be refractory to standard therapeutic interventions. If any life-saving intervention is to be attempted, then awareness of the syndrome and early clinical recognition will be of paramount importance to the treating clinician. Once the syndrome is suspected, treatment should include administration of antibacterial agents that decrease protein synthesis, such as clindamycin or linezolid. Adjunctive therapies, including intravenous immunoglobulin, monoclonal antibody preparations aimed at inhibiting pro-inflammatory cytokines, or medications that may induce hypothermia, such as general anesthesia, could be considered. Future treatment considerations could include medications that enhance thermoregulation or directly inhibit the pyrogenic activity of SE*l*-X and other pyrogenic toxins. We propose a case definition based on the current cases (see Table 1).

Table 1. Hyperpyrexic Toxic Shock Syndrome Proposed Case Definition

Clinical Criteria

1. Hyperthermia: An inexorable rise of temperature over 24 to 48 hours to greater than or equal to 108 °F (42.2 °C), refractory to all standard interventions to decrease temperature, and may or may not be preceded by intermittent fever.

2. Hypotension: Systolic blood pressure less than or equal to 90 mm Hg that is progressive and refractory (or only temporarily responsive) to all interventions.
3. Exclusion of other causes, such as neuroleptic malignant syndrome or malignant hyperthermia, on laboratory and/or clinical grounds.

Laboratory Criteria

1. Isolation of *S. aureus* from a normally sterile body site or respiratory secretions.
2. When *S. aureus* is isolated only from respiratory secretions, this must be accompanied by abnormal lung imaging suggestive of respiratory tract infection.
3. Cultures from normally sterile body sites are negative for alternative pathogens that would better explain the patient's clinical picture.

Probable Case: Meets all three clinical criteria

Confirmed Case: Meets all clinical and laboratory criteria

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Conflicts of Interest: The authors declare no conflict of interest.

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