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Extreme Pyrexia and Rapid Death Due to *Staphylococcus aureus* Infection: Analysis of Two Cases

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Abstract

Unusual *Staphylococcus aureus* infections in two patients are described. The infections are characterized by extreme pyrexia and rapid death. Both causative organisms produced a deletion mutant form of toxic shock syndrome toxin-1 and variant enterotoxin C which may have caused pyrexia and death.

Keywords

Staphylococcus aureus; Pyrexia; Superantigens

INTRODUCTION

Pyrogens elevate the temperature set point producing fever, a normal response to human infections. Although incompletely understood, fever is a regulated response as opposed to hyperthermia where there is a failure of thermoregulatory mechanisms [1,2]. Because the febrile response rarely, if ever, produces temperatures exceeding 42 °C (107.6 °F) [3], diagnoses such as malignant hyperthermia or neuroleptic malignant syndrome, in which there is a failure of thermoregulation, are entertained when temperatures exceed 41 °C (105.8 °F). Even in severe bacterial infections associated with production of potent pyrogens, such as staphylococcal toxic shock syndrome (TSS), temperatures exceeding 41.7 °C (107 °F) are uncommon or do not occur.

We report two cases of extreme pyrexia associated with *Staphylococcus aureus* which we believe represents a new syndrome most likely related to changes in pyrogenic toxin superantigens (SAgs). These patients had documented temperatures of ≥42.2 °C (108 °F), and unexpectedly rapid deaths. In one case, which did not involve prolonged hypotension, widespread tissue necrosis was seen with no obvious pathophysiologic explanation. Although one isolate was methicillin-susceptible (MSSA) and one methicillin-resistant (MRSA), they displayed similar SAg production.

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MATERIALS AND METHODS

S. aureus was identified as gram$^+$ cocci, catalase$^+$, and coagulase$^+$. Production of SAgs (TSS toxin-1 [TSST-1], staphylococcal enterotoxin B [SEB], and SEC) was assessed by antibody-based double immunodiffusion [4]. PCR for genes for TSST-1 (*tstH*), SEB (*seb*), and SEC (*sec*) was performed [5]; primers listed in Table 1.

CASE 1

A previously healthy 39 year old female presented to an outside hospital with back, hip, and abdominal pain, gradually worsening over the past week. Fever, nausea, and vomiting began in the past 24–48 hr. White blood cell count of $14 \times 10^3/\mu L$ and creatinine of 2.9 mg/dL were noted. A CT scan showed edema of the left psoas muscle thought to be a hemorrhage, and she was transferred to our institution. Upon questioning, the patient and family related a history of a recent fall and heavy use of ibuprofen for pain. Her temperature was 37 °C (98.2 °F), pulse 120 per minute, respirations 20 per minute, systolic blood pressure 135 mm Hg, and oxygen saturation 99% on room air. Her white blood cell count was $10.4 \times 10^3/\mu L$ with mild lymphopenia and slight left shift. Her hemoglobin was 12.4 g/dL and platelets $249 \times 10^3/\mu L$. The BUN was 43 mg/dL and creatinine 2.0 mg/dL. The international normalize ratio was 1.3, and the total creatine kinase was 1185 U/L. Chest x-ray showed no abnormalities, and repeat CT scan revealed ileopsoas region abnormalities, consistent with acute left retroperitoneal and pelvic hematoma. She was admitted to intensive care, and intravenous fluids, vancomycin, and ceftriaxone were begun. The patient remained hemodynamically stable except for some sinus tachycardia treated with intravenous metoprolol. Her oxygen requirements increased, and she required intubation and mechanical ventilation 11 hr after admission. Her temperature rose steadily since admission. Despite acetominophen, methylprednisolone, and application of a cooling blanket, her temperature increased to 106.5 °F (41 °C) rectally 13 hr after admission. Because she received succinylcholine during intubation earlier in the day, dantrolene was administered without effect. Subsequently, she became completely obtunded, and her systolic blood pressure rapidly decreased to 90 mm Hg and then 60 mm Hg. The cardiac resuscitation team was called and unsuccessful resuscitative measures undertaken. A peak temperature of 108 °F (42.2 °C) was recorded prior to death 14 hr after admission. The patient's peak temperature may have been higher but was not recorded. Two blood cultures revealed MRSA with intermediate susceptibility to fluoroquinolones and resistance to erythromycin. The organisms produced TSST-1 (6 ug/ml in vitro) and SEC (6 ug/ml) by antibody tests [4]. PCR indicated the strains contain *seb* and a deletion mutant of *tstH* [5]. Autopsy revealed acute kidney tubular and early hepatocellular necrosis, and left retroperitoneal cellulitis with associated fat necrosis. Large colonies of gram$^+$ cocci were noted along the peritoneal surface in the left retroperitoneum.

CASE 2

A 68 year old male presented to the emergency department with shortness of breath which worsened over the past 48 hr. He had extensive history of tobacco use, but quit 7 years previously. He carried a diagnosis of chronic obstructive pulmonary disease (COPD) and was on inhalers. His temperature was 37.8 °C (100 °F), pulse 154, respirations 45, systolic blood pressure 162 mm Hg, and initial oxygen saturation of 89% on room air. He appeared dyspneic, and had intermittent wheezing with rales and decreased breath sounds in the left lower lung fields. White blood cell count was $7.8 \times 10^3/\mu L$, hemoglobin 18.3 g/dL, and platelets $236 \times 10^3/\mu L$. The international normalized ratio was 1.3, and the creatinine 1.5 mg/dL. Initial blood gas analysis on 50% FiO_2 showed a pH of 7.32, total CO_2 of 17 mmol/L, pCO_2 of 31 mm Hg, and pO_2 of 63 mm Hg. Tests for influenza A and B antigens were negative. Initial chest x-ray revealed extensive infiltrates in the left lower lobe. CT angiography revealed extensive

infiltrates involving the entire left lung but no pulmonary emboli. Levofloxacin, vancomycin, and methylprednisolone were administered. He was then admitted to intensive care with diagnosis of severe community acquired pneumonia and COPD exacerbation. Shortly after admission, he required intubation and mechanical echanical ventilation. Hypotension developed which initially responded to norepinepherine and intravenous fluids. Vancomycin and levofloxacin were discontinued and linezolid, ceftriaxone, and drotrecogin alpha were begun. His hypotension progressively worsened. Vasopression, and subsequently, phenylepherine were added. Despite continuation of methylprednisolone, administration of acetaminophen, and application of a cooling blanket, his temperature rose to 40 °C (104 °F), peaking at 42.3 °C (108.3 °F) rectally 19 hr after admission. He had received no medications associated with malignant hyperthermia syndrome. Adequate oxygen saturation was maintained on FiO2 of 60%. Shortly thereafter, he became acutely hypotensive with pulseless electrical activity, and the cardiac resuscitation team was called. Resuscitative efforts were initially successful with systolic blood pressure rising above 100 mm Hg. However, the patient again became hypotensive and, despite maximal vasopressor support, further resuscitative efforts were unsuccessful; the patient expired 20 hr after admission. The patient's family declined autopsy. Tracheal aspirate culture yielded heavy growth of MSSA with intermediate susceptibility to flouroquinolones, while blood cultures obtained on admission remained negative. The *S. aureus* isolate produced TSST-1 (6 ug/ml in vitro) and SEC (6 ug/ml) [4]. PCR indicated the presence of *seb* and a deletion mutant of *tstH* [5].

DISCUSSION

Morbidity and mortality from *S. aureus* is not unexpected. These two cases, however, exhibit unique features, which represent departures from typical *S. aureus* disease. Notably, there were documented temperatures of ≥42.2 °C (108 °F). High temperatures can be seen with bacterial infections. Nonetheless, elevations to this degree are unusual. Autopsy performed on the first patient revealed widespread tissue necrosis with no obvious pathophysiologic correlate. Hyperthermia can be fatal, inducing widespread cytotoxicity and could explain these findings [6]. However, temperatures of 42 °C (107.6 °F) have been deliberately induced in humans without ill effects [7]. Thus, it is more likely that additive effects of hyperthermia, sepsis, and SAgs are the cause of the observed cytotoxicity. The second patient had a temperature of 42.3 °C (108.2 °F) despite substantial doses of methylprednisolone, and refractory hypotension without concomitant bacteremia. These are not typical features of *S. aureus* infection and suggest altered patterns or effects of SAgs.

We evaluated the causative organisms for SAgs; both were TSST-1^+ and SEC^+ by antibody tests [4]. This SAg combination is observed in 15% of TSS isolates [8]. However, our studies suggest these stains, which appear as CDC USA300 [9], produce a deletion mutant of TSST-1 and variant SEC. PCR followed by sequencing [5] indicates the encoded TSST-1 has a deletion encompassing its N-terminal half; the mutant protein has a predicted molecular weight of 13,000 (shortened by 72 amino acids) versus 22,000 for native TSST-1. This deletion disrupts the major histocompatibility complex II-binding domain [10], despite the toxin maintaining antibody reactivity. Part of the T cell receptor-binding site is conserved [10]. Administration of cell-free culture supernates (2 ml/rabbit) intravenously was pyrogenic (rectally at 3–4 hr, 42.5 °C [108.5 °F] ± 0.15 °C), rapidly and uniformly lethal (5–6 hr, 6/6 succumbed), but fever and lethality were neutralized by immunization or passive antibodies against native TSST-1 (0/6 succumbed, $p<0.001$ compared to controls, Fishers Exact). This suggests these strains produce a mutant of TSST-1, which increases virulence, inducing extreme pyrexia and lethality. We do not know if activity occurs through superantigenicity or novel effects such as direct neurotoxicity toxicity; the mutant retains 60% of native TSST-1 superantigenicity.

We have not studied the SEC variation, and we have not assessed SEC activity in rabbits. However, the SEC may be less important in rabbits since antibodies against TSST-1 provide complete protection from culture supernate challenge. PCR indicates the strains lack *sec*, even though antibody tests suggest SEC protein production. PCR indicates the strains contain *seb*, highly related to *sec*, but antibody tests are negative for SEB. Based on the greater specificity of antibody reactivity versus PCR, we suggest the strains make a variant SEC.

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Table 1

PCR primers used for detection of superantigen genes

Gene Detected	Primer Name	Sequence (5' to 3')	Product Size
seb	SEB Primer 1 SEB Primer 2	CACCCAACGTTTTAGCAGAGAG GCCTGCACCAGGAGATAAATTTGACC	765bp
sec	SEC Primer 1 SEC Primer 2	GAGTCAACCAGACCCTATGCC CGCCTGGTGCAGGCATC	610bp
tstH	TSST-1 Primer 1 TSST-1 Primer 2	GTAAGCCCTTTGTTGCTTGC GCGTTACAAATACTGA	731bp

Note: bp, base pairs