Chapter 14

STAPHYLOCOCCAL ENTEROTOXIN B AND RELATED TOXINS

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INTRODUCTION

The gram-positive bacteria *Streptococcus pyogenes* and *Staphylococcus aureus* extensively colonize the human population and are frequent opportunistic pathogens. These bacteria secrete a variety of enzymatic and nonenzymatic virulence factors that are responsible for many disease symptoms. Among these factors, staphylococcal enterotoxins (SEs), toxic shock syndrome toxin (TSST-1), and streptococcal pyrogenic exotoxins of *S pyogenes* share a common three-dimensional protein fold characteristic of the bacterial products called "superantigens" because of their profound effects upon the immune system. Most strains of *S aureus* and *S pyogenes* examined harbor genes for superantigens and are likely to produce at least one of these products. The staphylococcal enterotoxins are most frequently associated with food poisoning, yet not all superantigens are enterotoxins, and more severe physiological consequences, such as a life-threatening toxic shock syndrome, may result from exposure to any of the superantigens through a nonenteric route. High dose, microgram-level exposures to staphylococcal enterotoxin B (SEB) will result in fatalities, and inhalation exposure to nanogram or lower levels may be severely incapacitating.[1] In addition, the severe perturbation of the immune system caused by superantigen exposure may lower the infectious or lethal dose of replicating agents such as influenza virus.[2]

SEB is a prototype enterotoxin and potential biological threat agent produced by many isolates of *S aureus*. During the 1960s, SEB was studied extensively as a biological incapacitant in the US offensive program. US scientists had completed studies that clearly demonstrated the effectiveness of SEB as a biological weapon before the ban on offensive toxin weapons announced by President Nixon in February 1970 (3 months after replicating agent weapons were banned). SEB was exceptionally suitable as a biological agent because its effect was produced with much less material than was necessary with synthetic chemicals, and it presumably had an exceptional "safety ratio" (calculated by dividing the effective dose for incapacitation by the dose producing lethality). However, the safety ratio is misleading because the coadministration of SEB or related toxins with replicating pathogens may profoundly lower the lethal dose. Available countermeasures and diagnostics have focused on SEB because of its historical significance in past biowarfare efforts; however, SEB represents many (perhaps hundreds) of related biologically active superantigens that are readily isolated and manipulated by recombinant DNA techniques. All of these superantigens are presumed to have a similar mode of biological action, but very little data are available for confirmation.

DESCRIPTION OF THE AGENT

An examination of genes encoding superantigens of *S aureus* and *S pyogenes* indicates a common origin or perhaps an exchange of genetic elements between bacterial species. The great diversity of superantigens and the highly mobile nature of their genetic elements also suggest an accelerated rate of evolution. Staphylococcal and streptococcal strains that colonize domestic animals are potential genetic reservoirs for new toxin genes,[3] and the transfer of these sequences may contribute to hybrid polypeptides. However, the many similarities among severe diseases caused by *S aureus* and *S pyogenes* superantigens[4] imply a common mechanism of pathology. Amino acid sequence comparisons indicate that superantigens can be loosely compiled into three major subgroups and numerous sequence variations[5]; whereas genetic analysis shows that they are all likely derived from common ancestral genes. Despite significant sequence divergence, with similarities as low as 14%, overall protein folds are similar among staphylococcal and streptococcal superantigens. The toxin genes have evolved by strong selective pressures to maintain receptor-binding surfaces by preserving three-dimensional protein structure. The contact surfaces with human leukocyte antigen DR (HLA-DR) receptors involve variations of conserved structural elements,[6,7] which include a ubiquitous hydrophobic surface loop, a polar-binding pocket present in most superantigens, and one or more zinc-binding sites found in some toxins. Comparison of antibody recognition among superantigens[8] suggests that antigenic variation is maximized while three-dimensional structures, and hence receptor-binding surfaces, are conserved. From a practical standpoint, this observation indicates that a large panel of antibody probes will be required for proper identification of samples.

Molecular details of the biological actions of bacterial superantigens are well established. Superantigens target cells mediating innate and adaptive immunity, resulting in an intense activation and subsequent pathology associated with aberrant host immune responses. Class II molecules of the major histocompatibility complex (MHC) are the primary receptors, and the MHC-bound superantigen in turn stimulates T cells. Most superantigens share a common mode for binding class II MHC molecules, with additional stabilizing interactions that are unique to each one.[9]

A second, zinc-dependent molecular binding mode for some superantigens increases T-cell signaling and may impart greater toxicities in some cases. In normal T-cell responses to peptide antigens, the CD4 molecule stabilizes interactions between T-cell antigen receptors and class II MHC molecules on antigen-presenting cells (Figure 14-1). Superantigens also cross-link T-cell antigen receptors and class II MHC molecules, mimicking the CD4 molecule,[10] and hence stimulate large numbers of T cells. In addition, each superantigen preferentially stimulates T cells bearing distinct subsets of antigen receptors, predominantly dictated by the specific Vβ chain. An intense and rapid release of cytokines such as interferon-γ, interleukin-6 and tumor necrosis factor-α is responsible for the systemic effects of the toxins.[11] In addition to direct T-cell activation, the gastrointestinal illness especially prominent after ingestion of staphylococcal enterotoxins is also associated with histamine and leukotriene release from mast cells.[12] Furthermore, the CD44 molecule reportedly provides protection from liver damage in mice caused by SEB exposure through a mechanism linked to activation-induced apoptosis of immune cells.[13]

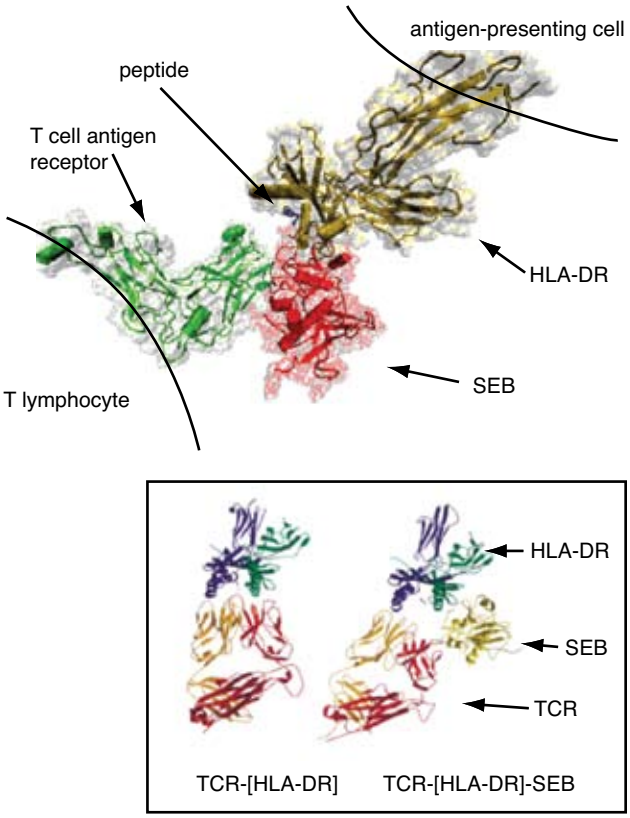

Fig. 14-1. Molecular model of receptor binding. Staphylococcal enterotoxins and other bacterial superantigens target the multireceptor communication between T cells and antigen-presenting cells that is fundamental to initiating pathogen-specific immune clearance. The superantigen inserts itself between the antigen receptor of T cells and the class II major histocompatibility complex molecule displaying peptides from potential pathogens. Toxin exposure results in hyperactivation of the immune system, and the pathology is mediated by tumor necrosis factor-α, interferon-γ, and other cytokines.
HLA-DR: human leukocyte antigen DR
SEB: staphylococcal enterotoxin B
TCR: T cell receptor

Individuals within the human population may respond differently to superantigen exposure as a result of MHC polymorphisms, age, and many physiological factors. Each toxin exhibits varying affinities toward the HLA-DR, DQ, and DP isotypes and distinct alleles of class II MHC molecules, observed by differences in T-cell responses in vitro. In addition, primates, including humans, are most sensitive to superantigens compared to other mammals.[14] Lethal or incapacitating doses of toxin may be lowered by coexposure to endotoxin from gram-negative bacteria[11] or hepatotoxins,[15] or by infection with replicating agents.[2]

Rodents and other domestic animals infected with strains that produce TSST-1 and SE[16,17] are potential environmental reservoirs. Both ovine- and-bovine specific staphylococcal toxins, which are associated with mastitis, are almost identical to TSST-1 in amino acid sequence.[18] Toxigenic strains are frequent or universal in both clinical and nonclinical isolates of *S aureus* and *S pyogenes*, and these strains contribute significantly to several diseases. Approximately 50% of nonmenstrual toxic shock syndrome (TSS) cases are linked to TSST-1, while the remaining cases are attributable to SE, with SEB predominating.[19] Kawasaki's syndrome and some forms of arthritis are loosely associated with organisms producing streptococcal pyrogenic exotoxins (SPEs), SEA, and TSST-1.[20] In addition, streptococcal pneumonia with accompanying TSS-like symptoms is caused by SPE-producing bacteria.[21]

Most of the streptococcal superantigens are encoded by mobile genetic elements. SPE-A, SPE-C, SEA, and SEE are all phage-borne, while SED is plasmid-encoded. A chromosomal cluster of SE and SE-like genes is present in strains of *S aureus*.[22] Because little evidence of genetic drift exists, it has been hypothesized that the majority of staphylococcal and streptococcal TSS-like bacterial isolates have each descended from single clones.[23] Production of many SEs is dependent on the phase of cell-growth cycle, environmental pH, and glucose concentration. Transcriptional control of TSST-1, SEB, SEC, and SED is mediated through the accessory gene regulator (agr) locus,[24] whereas SEA expression appears to be independent of agr. Strains that are agr-negative are generally low toxin producers.

However, there are also considerable differences in production levels among agr-positive isolates. In addition, a feedback-mediated regulatory mechanism for increasing expression of SEB and TSST-1 and suppressing all other exotoxins has been demonstrated.[25]

At the cellular level, the interaction of superantigens with receptors on antigen-presenting cells and T cells leads to intracellular signaling.[26] High concentrations of SEB elicit phosphatidyl inositol production and activation of protein kinase C and protein tyrosine kinase pathways,[26–28] similar to mitogenic activation of T cells. SEs also activate transcription factors NF-κB and AP-1, resulting in the expression of proinflammatory cytokines, chemokines, and adhesion molecules. Both interleukin-1 and tumor necrosis factor-α can directly activate the transcription factor NF-κB in many cell types, including epithelial cells and endothelial cells, perpetuating the inflammatory response. Another mediator, interferon-γ, produced by activated T cells and natural killer cells, synergizes with tumor necrosis factor-α and interleukin-1 to enhance immune reactions and promote tissue injury. The substances induced directly by SEB and other superantigens—chemokines, interleukin-8, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and macrophage inflammatory protein-1β—can selectively chemoattract and activate leukocytes. Thus, cellular activation by SEB and other superantigens leads to severe inflammation, hypotension, and shock. Additional mediators contributing to SEB-induced shock include prostanoids, leukotrienes, and tissue factor from monocytes; superoxide and proteolytic enzymes from neutrophils; tissue factor; and chemokines from endothelial cells. Activation of coagulation via tissue factor leads to disseminated intravascular coagulation, tissue injury, and multiorgan failure. SE-induced TSS thus presents a spectrum and progression of clinical symptoms, including fever, tachycardia, hypotension, multiorgan failure, disseminated intravascular coagulation, and shock.

Given the complex pathophysiology of toxic shock, the understanding of the cellular receptors and signaling pathways used by staphylococcal superantigens, and the biological mediators they induce, has provided insights to selecting appropriate therapeutic targets. Potential targets to prevent the toxic effects of SEs include (*a*) blocking the interaction of SEs with the MHC, TCRs,[26] or other costimulatory molecules[29–32]; (*b*) inhibition of signal transduction pathways used by SEs[26]; (*c*) inhibition of cytokine and chemokine production[33,34]; and (*d*) inhibition of the downstream signaling pathways used by proinflammatory cytokines and chemokines.

Most therapeutic strategies in animal models of SEB-induced shock have targeted proinflammatory mediators. Therapeutic regimens include corticosteroids and inhibitors of cytokines, caspases, or phosphodiesterases. Although several clinical trials of treatment of sepsis with high-dose corticosteroids were unsuccessful, a multicenter clinical trial using lower doses of corticosteroids for longer periods reduced the mortality rate of septic shock.[35] A newer intervention targeting the coagulation pathway by activated protein C improved the survival of septic patients with high APACHE (Acute Physiology and Chronic Health Evaluation, a system for classifying patients in the intensive care unit) score.[36] Because coagulation and endothelial dysfunction are important facets of SEB-induced shock, activated protein C may also be useful in treating TSS.

Limited therapeutics for treating superantigen-induced toxic shock are currently available. Intravenous immune globulin was effective as a treatment in humans after the onset of TSS. Antibody-based therapy targeting direct neutralization of SEB or other superantigens represents another form of therapeutics, most suitable during the early stages of exposure before cell activation and the release of proinflammatory cytokines. Because some neutralizing antibodies cross-react among different superantigens,[8] a relatively small mixture of antibodies might be effective in treating exposures to a greater variety of superantigens. Vaccines of SEB and SEA with altered critical residues involved in binding class II MHC molecules were also used successfully to vaccinate mice and monkeys against SEB-induced disease.[37,38]

PATHOGENESIS

Rhesus macaques (*Macaca mulatta*) have been used extensively as a model for lethal disease caused by inhaled SEB. Rabbits, endotoxin-primed mice, and additional animal models have been developed. Because SEB and related toxins primarily affect primates, the following unpublished rhesus monkey data are highly relevant for understanding potential human pathology. Young and mature adult male and female rhesus monkeys developed signs of SEB intoxication[39] after being exposed to a lethal dose of aerosolized SEB for 10 minutes in a modified Henderson head-only aerosol exposure chamber.[40] These animals demonstrated no detectable anti-SEB antibody before exposure. After inhalation exposure, microscopic lymphoproliferation of T-cell–dependent areas of the lymphoid system, consistent with the potent stimulatory effect of SEB

on the rhesus monkey immune system, was apparent. Immunohistochemical analysis, using anti-CD3 antibody, of the large lymphocytes present in the pulmonary vasculature of the monkeys identified these lymphocytes as T cells.[41]

Generally, the SEB-intoxicated rhesus monkeys developed gastrointestinal distress within 24 hours postexposure. Clinical signs were mastication, anorexia, emesis, and diarrhea. After mild, brief, self-limiting gastrointestinal signs, the monkeys had a variable period of up to 40 hours of clinical improvement. At approximately 48 hours postexposure, the monkeys generally had an abrupt onset of rapidly progressive lethargy, dyspnea, and facial pallor, culminating in death or euthanasia within 4 hours of onset.

At necropsy, most of the monkeys had similar gross pulmonary lesions. The lungs were diffusely heavy and wet, with multifocal petechial hemorrhages and areas of atelectasis. Clear serous-to-white frothy fluid often drained freely from the laryngeal orifice. The small and large intestines frequently had petechial hemorrhages and mucosal erosions. Typically, the monkeys had mildly swollen lymph nodes, with moist and bulging cut surfaces.

Most of the monkeys also had similar microscopic pulmonary lesions. The most obvious lesion was marked multifocal to coalescing interstitial pulmonary edema involving multiple lung lobes. Peribronchovascular connective tissue spaces were distended by pale, homogeneous, eosinophilic, proteinaceous material (edema), variably accompanied by entrapped, beaded fibrillar strands (fibrin), extravasated erythrocytes, neutrophils, macrophages, and small and large lymphocytes. Perivascular lymphatics were generally distended by similar eosinophilic material and inflammatory cells. Most of the monkeys had intravascular circulating and marginated neutrophils, monocytes, mononuclear phagocytes, and lymphocytes, including large lymphocytes with prominent nucleoli (lymphoblasts), some in mitosis (Figure 14-2). Extravascular extension of these cell types was interpreted as exocytosis / chemotaxis.

Loss of airway epithelium was inconsistent. Some monkeys had multifocal, asymmetric denudation of bronchial epithelium, with near total loss of bronchiolar epithelium. Former bronchioles were recognized only by their smooth muscle walls. Scant bronchial intraluminal exudate consisted of mucoid material, neutrophils, macrophages, and sloughed necrotic cells.

A common finding was multifocal alveolar flooding and acute purulent alveolitis. Alveolar septa were distended by congested alveolar capillaries. Alveolar spaces were filled with pale, homogeneous, eosinophilic material (edema), with deeper embedded eosinophilic beaded fibrillar strands (fibrin), or with condensed, curvilinear, eosinophilic deposits hugging the alveolar septal contours (hyaline membranes). A variably severe cellular infiltrate of neutrophils, eosinophils, small lymphocytes, large lymphocytes (lymphoblasts), erythrocytes, and alveolar macrophages filled alveolar spaces. Replicate pulmonary microsections stained with phosphotungstic-acid–hematoxylin demonstrated alveolar fibrin deposition. Replicate microsections stained with Giemsa revealed scarce sparsely granulated connective-tissue mast cells.

In the upper respiratory tract, the tracheal and bronchial lamina propria was thickened by clear space or pale, homogeneous, eosinophilic material (edema), neutrophils, small and large lymphocytes, and (possibly preexisting) plasma cells. The edema and cellular infiltrate extended transtracheally into the

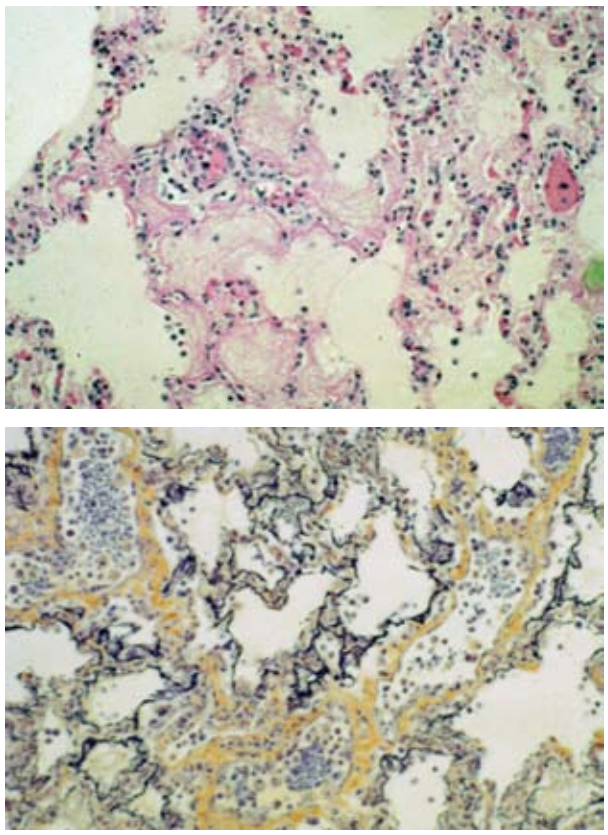

Fig. 14-2. Lung of a rhesus monkey that died from inhaled staphylococcal enterotoxin B. (**a**) Marked perivascular interstitial edema and focal loss of bronchial epithelium can be seen (hematoxylin-eosin stain, original magnification x 10). (**b**) The intravascular mononuclear cells include lymphocytes, lymphoblasts, monocytes, and mononuclear phagocytes (hematoxylin-eosin stain, original magnification x 50).

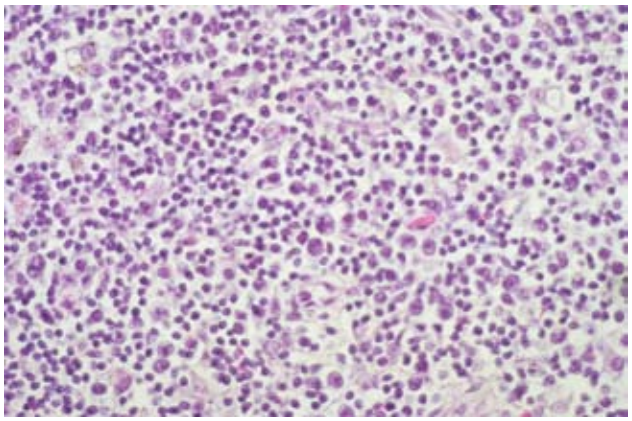

Fig. 14-3. Mediastinal lymph node of a rhesus monkey that died from inhaled staphylococcal enterotoxin B. Paracortical lymphoproliferation with lymphoblasts can be seen (hematoxylin-eosin stain, original magnification x 100).

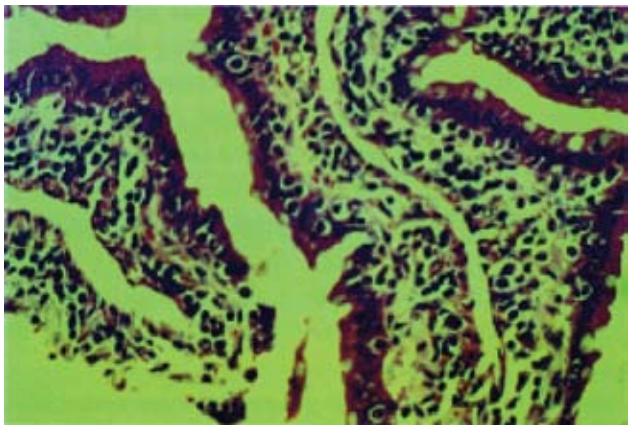

Fig. 14-4. Small intestine of a rhesus monkey that died from inhaled staphylococcal enterotoxin B. Intraepithelial lymphoblastic leukocytes can be seen (hematoxylin-eosin stain, original magnification x 100).

mediastinum, with moderate to marked mediastinal lymphangiectasia.

Lymphoid tissues of the respiratory tract had depletion of B-cell–dependent areas and hyperplasia of T-cell–dependent areas. The bronchus-associated lymphoid tissue in some of the monkeys had follicular lymphocytic depletion. Most of the mediastinal lymph nodes had subcapsular and medullary sinus edema, histiocytosis, and paracortical lymphoid hyperplasia, characterized by numerous closely packed small lymphocytes with interspersed macrophages bearing tingible bodies and large lymphocytes having prominent nucleoli (lymphoblasts) (Figure 14-3). There were scattered mitoses, including atypical mitoses. Cortical follicles had small solid centers or hypocellular, hyalinized (depleted) centers.

Microscopic changes in lymphoid tissues elsewhere in the body mirrored changes in the respiratory mucosal lymphoid tissue. Mesenteric, axillary, inguinal, and retropharyngeal lymph nodes had sinus edema and histiocytosis, paracortical lymphocytic and lymphoblastic hyperplasia, and unstimulated or depleted follicular centers. Also depleted were follicular germinal centers of gut-associated lymphoid tissue. Splenic T-cell–dependent periarteriolar sheath zones were hypercellular, populated by a mix of small and large lymphocytes and macrophages, whereas B-cell–dependent follicular areas were not recognized. Several monkeys had marked diffuse depletion of cortical thymocytes, with a "starry sky" appearance attributed to the presence of numerous thymic macrophages bearing tingible bodies.

Many of the monkeys had a mild erosive enterocolitis, with slight, superficial, multifocal mucosal loss and with numerous lamina proprial macrophages bearing engulfed cellular debris. Crypt enterocytes had a high nuclear-to-cytoplasmic ratio and numerous mitoses. The crypt epithelium had a conspicuous population of large mononuclear intraepithelial leukocytes interpreted as lymphoblasts (Figure 14-4). In the colon of some monkeys, there were many small crypt abscesses.

Generalized vascular changes in most of the monkeys were congestion, swollen endothelial cells with many large intravascular lymphocytes or lymphoblasts and inconsistent widening of perivascular connective tissue spaces (by edema). Hepatic lesions were portal infiltrates of lymphocytes, lymphoblasts, macrophages, and occasional neutrophils. The choroid plexus was slightly thickened by edema.

CLINICAL DISEASE

The clinical documentation of TSS provides perhaps the most comprehensive source of information on the pathology of superantigen (eg, SEB) exposure. To meet the strict Centers for Disease Control and Prevention criteria for TSS,[42] negative blood (except for *S aureus* or *S pyogenes*), throat, or cerebrospinal fluid cultures, as well as negative serologic tests for Rocky Mountain spotted fever, leptospirosis, and measles should be obtained. Although TSS disease symptoms are well established, characterized by a rapid drop in blood pressure, elevated temperature, and multiple organ failure, the respiratory route of exposure may involve some unique mechanisms.

The profound hypotension and desquamation of the palms and soles of the feet that are characteristic of TSS are not observed in exposure by inhalation, and respiratory involvement is rapid, unlike in other forms of TSS. Furthermore, the fever prominent after aerosol exposure is generally not observed in cases of SEB ingestion.

Documentation of an accidental laboratory inhalation exposure of nine laboratory workers to SEB best exemplifies the clinical disease, described as a severely incapacitating illness of rapid onset (3–4 hours) and modest acute duration (3–4 days).[43]

Fever

Fever was prominent in all nine of those exposed. Eight of the individuals experienced at least one shaking chill that heralded the onset of illness. Using the morning peak level of SEB aerosol generation in the laboratory as the most likely time of exposure, onset of fever occurred from 8 to 20 hours post initial exposure, with a mean time of onset of 12.4 ± 3.9 (SD) hours. Duration of fever was from 12 to 76 hours after onset, with a mean duration of 50 ± 22.3 hours. Fever ranged as high as 106° acutely. Myalgias were often associated with the initial fever. Onset of myalgia was between 8 and 20 hours, with a mean onset of 13 ± 5 hours. Duration was from 4 to 44 hours, and the mean duration was 16 ± 15 hours.

Respiratory Symptoms

All nine patients were admitted to the hospital with a generally nonproductive cough. Onset was at 10.4 ± 5.4 hours, and duration was 92 ± 41 hours. Five had inspiratory rales with dyspnea. The three most seriously compromised patients had dyspnea, moist inspiratory and expiratory rales, and orthopnea that gradually cleared. One individual had profound dyspnea for the first 12 hours that moderated to exertional dyspnea and rales, which persisted for 10 days. Chest radiographs on admission showed densities compatible with "patches of pulmonary edema" and Kerley lines suggesting interstitial edema. During recovery, discoid atelectasis was noted. Moderate compromise of the respiratory system was often accompanied by radiographic evidence of peribronchial accentuation or "cuffing." The mildly ill patients had normal radiographs. One of the three severely ill patients had severe pulmonary compromise and profound dyspnea and received only slight relief when treated with an aminophylline suppository. Moderately intense chest pain, of a substernal pleuritic type, occurred in seven individuals. Onset of chest pain was at 12 ± 6.5 hours and lasted for 4 to 84 hours, with a mean duration of 23 ± 27 hours.

Headache

Eight of the nine patients experienced headache. Onset ranged from 4 to 36 hours, and the mean time of onset was at 13.3 ± 10 hours. Duration ranged from 8 to 60 hours, with a mean duration of 30.6 ± 19 hours. The headaches ranged from severe to mild, but were usually mild by the second day of hospitalization. Five individuals' headaches responded to Darvon (propoxyphene hydrochloride; Eli Lilly & Co, Indianapolis, Ind) or codeine.

Nausea and Vomiting

Gastrointestinal symptoms occurred in more than half of the individuals, nausea and anorexia in six, and vomiting in four. The onset of nausea ranged from 8 to 24 hours, with a mean onset of 17 ± 6.3 hours. Duration ranged from 4 to 20 hours, with a mean of 9 ± 5.5 hours. The time to onset of anorexia ranged from 8 to 24 hours with a mean onset of 18.5 ± 5.6 hours. Duration of anorexia ranged from 4 to 136 hours, and the mean duration was 44.5 ± 45 hours. Vomiting occurred in four patients, sometimes after prolonged paroxysms of coughing. The range of onset of vomiting was 8 to 20 hours, with a mean time to onset of 14 ± 5.1 hours. Duration was not prolonged and usually consisted of one episode. The patients were successfully treated with Compazine (prochlorperazine; SmithKline Beecham Pharmaceuticals, Philadelphia, Pa) and Benadryl (diphenhydramine hydrochloride; Pfizer Pharmaceuticals Company, New York, NY). Only one individual demonstrated hepatomegaly and bile in the urine, although another patient also demonstrated mildly elevated liver-function tests. No diarrhea was reported in any of the exposed individuals.

Other Signs and Symptoms

Cardiovascular

All patients who experienced chest pain had normal electrocardiograms. Throughout the illness, all patients were normotensive. Vomiting was of brief duration, and no one, including those vomiting, required intravenous fluid administration. The patients' pulse rates, when elevated, paralleled temperature elevation.

Hematology

Leukocytosis was observed in most of the patients 12 to 24 hours after exposure to the toxin.

Ocular Effects

None of the patients experienced conjunctivitis, although one individual later stated he remembered that his eyes had "burned" during the believed time of exposure. This contrasts with reports of conjunctivitis resulting from separate accidental laboratory exposures.[44]

DETECTION AND DIAGNOSIS

The staphylococcal enterotoxins are moderately stable proteins; therefore, immunological evaluation should be possible in field or clinical samples. A variety of rapid and sensitive detection methods are available.[45,46] Immunoassays can detect picogram quantities of toxins in environmental samples. Plasma concentrations of superantigens were measured in septic patients of an intensive care unit using an enzyme-linked immunosorbent assay.[47] In one study, [48] the mean concentration of TSST-1 in human sera from TSS patients was reported to be 440 pg/mL. In contrast, anti-TSST-1 antibody titers are often low in TSS patients[49,50] and only recover during convalescence. Furthermore, most normal human serum samples contain detectable levels of antibody reacting with several different toxins, including SEB. Therefore, serum antibody titers are of little diagnostic value. If bacterial sepsis is suspected and cultures can be obtained, detecting minute quantities of potentially toxigenic strains is possible by using polymerase chain reaction amplification and toxin gene-specific oligonucleotide primers. The results from both polymerase chain reaction and immunoassays are rapid, allowing quantitative or qualitative measurements in less than 24 hours. Finally, as the best approach to early diagnosis on the battlefield, toxins may be identifiable in nasal swabs from individuals exposed to aerosols for at least 12 to 24 hours postexposure.

MEDICAL MANAGEMENT

No specific therapy has been identified or described. Supportive therapy in the nine mild accidental exposure cases described above seemed to provide adequate care. Symptoms of fever, muscle aches, and arthralgias may respond to cool compresses, fluids, rest, and judicious use of acetaminophen or aspirin. For nausea, vomiting, and anorexia, symptomatic therapy should be considered. Antihistamines (eg, diphenhydramine) and phenothiazine derivatives (eg, prochlorperazine) have been used parenterally or as suppositories. The success of these drugs in controlling nausea may have been augmented by the relatively short duration of nausea and vomiting induced by aerosolized SEB. Because of the brevity of vomiting episodes, fluid replacement was not considered or required in the series discussed. However, replacement may be necessary in the event of prolonged vomiting resulting in fluid and electrolyte depletion. Diarrhea was not observed in human accidental exposure cases, but deposition of toxin on foodstuffs could produce the syndrome, which should be treated symptomatically.

Initial symptomatic therapy with cough suppressants containing dextromethorphan or codeine should be routinely employed. Prolonged coughing unrelieved by codeine might benefit from a semisynthetic centrally acting narcotic antitussive containing hydrocodone (dihydrocodeinone).

Pulmonary status should be monitored by pulse oximetry, and when respiratory status is compromised, prompt evacuation to a site with capacity for intensive respiratory care by mechanical ventilation should be considered.

IMMUNOTHERAPY

Infusion of intravenous immunoglobulin has been successfully used[51,52] to treat episodes of Kawasaki's syndrome linked to SE and TSST-1. An anecdotal case of TSS with elevated TSST-1 and SEA levels, complicated by life-threatening multiorgan dysfunction, was successfully treated by early introduction of plasma exchanges.[53] Unpublished studies have documented the prophylactic and therapeutic value of human intravenous immunoglobulin in rhesus monkeys after inhalation of SEB, prescribed to the presence of antibodies to SE and TSST-1 in commercial preparations of intravenous immunoglobulin and normal human sera. Prior exposure to SEB by inhalation does not appear to protect against a subsequent episode. However, increased antibody titers to SEB are protective, and efforts to devise both passive and active immunotherapy show promise. Because of the rapidity of receptor binding by these toxins (apparent saturation < 5 min), active immunity should be considered as the best defense.

VACCINES

A formalin-treated SEB toxoid demonstrated some degree of efficacy in animal trials, but is not approved for human use. Vaccines produced by site-specific mutagenesis of the toxins, delivered by intramuscular or interdermal routes, have also shown promising results in animal trials. These recombinant subunit vaccines were produced by substitution of active receptor-binding amino acid side chains that reduced affinities and consequential T-cell activation,[7,9,37,38] without altering the three-dimensional structure of the antigen. Though promising, these engineered vaccines are not yet licensed or available for general use.

SUMMARY

SEB is representative of a group of bacterial proteins that exerts profound toxic effects upon the immune system. Many sensitive immunoassays have been developed for laboratory detection of most of the staphylococcal and streptococcal superantigen toxins, but the limit of field detection is unknown. Inhalation exposure to agents such as SEB may result in severe but temporary incapacitation, while high-dose exposures will result in fatalities. Supportive symptomatic therapy is the only known method of treatment. Vaccines currently under development may afford protection to individuals but are not yet licensed for human use.

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