[Frontiers in Bioscience 13, 4009-4014, May 1, 2008]

Anthrax-associated shock

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1. ABSTRACT

Recent events have brought attention to the potential of *Bacillus anthracis* as an agent of bioterrorism. The shock like state of anthrax is invariably associated with high mortality, despite anti-microbial and supportive therapy. Multi-system dysfunction is typical, including: enhanced vascular permeability, hemorrhage and inflammation. Important questions concerning the pathophysiology of anthrax-associated shock remain unanswered, including the effects of *B. anthracis* infection on cardiac function. This review discusses the current state of knowledge regarding the pathophysiology of anthrax-associated shock.

2. BACKGROUND

2.1. Introduction

Anthrax is a zoonosis that often causes death in affected humans. Anthrax is a disease known since antiquity, but by the late 20th century human anthrax had become extremely rare, at least in developed countries. The causative agent, *B. anthracis*, has gained recent notoriety as a potential biological weapon because it can be easily dispersed by aerosols to produce inhalational disease. Inhalational anthrax is rapidly progressive. Affected individuals often develop non-specific respiratory symptoms that quickly evolve to prostration and death with overwhelming bacteremia. A shock-like condition

accompanies the late phase of anthrax and carries with it an extremely high mortality despite antibiotic treatment and supportive care. This in part is believed to be related to the central role of toxin in this process. In 1979, the accidental release of *B. anthracis* spores from a military facility in the former Soviet Union in 1979 resulted in 69 associated deaths (1). In 2001, *B. anthracis* spores delivered by mail resulted in 11 cases of anthrax of whom 5 died. While the clinical features of *B. anthracis*-induced shock share many of the features of shock induced by other microbes, many aspects of this process are poorly understood. For example, in contrast to endotoxin-mediated sepsis, the role of pro-inflammatory cytokine storm has not been definitively established. In this review, we discuss the pathogenesis of anthrax with particular attention to the basis of *B. anthracis*-induced shock and the associated hemodynamic dysfunction.

2.2. Epidemiology

Anthrax is a disease of animals and in particular herbivores such as sheep and cattle, though carnivores may also be affected. Animals acquire *B. anthracis* infection via exposure to contaminated soil, where the organism persists in spore form. Animals also acquire infection from biting insects. Affected animals develop a bleeding diathesis as manifested by bleeding from the nose, vagina and anus, then die suddenly. Apart from cases associated with its use as biologic agent, human cases of anthrax result from exposure to infected animals or contaminated animal products, including: hides, raw meat, hair and bone meal. In the past, outbreaks of the disease in people working in woolen mills (wool sorter's disease) were commonly described in the U.S. Naturally-acquired human anthrax has largely been eliminated from developed countries through animal vaccination programs and veterinary-supervised care of affected animals.

2.3. Microbiology

Anthrax is caused by the bacteria *Bacillus anthracis*, a gram-positive spore-forming rod that grows in long chains. The bacterium is aerobic and grows well on conventional media producing opaque white, non-hemolytic colonies on Sheep Red Blood Cell Agar. B anthracis can be distinguished from more common species of Bacillus (e.g. cereus) by biochemical and molecular assays.

2.3.1. Spores

The spores of *B. anthracis* are centrally located in the bacterium and appear unstained in Gram stain preparations. A loosely fitting membrane known as the exopsorium covers the spore. The spore is resistant to a wide range of harsh conditions (e.g., drying, heat and disinfectants), thus allowing the organism to persist for prolonged intervals within the environment. *B. anthracis* spores are infectious and germinate after phagocytosis by effector cells, (e.g. macrophages) within the lung and gastrointestinal tract. The current view of anthrax pathogenesis involves inhalation of *B. anthracis* spores, ingestion by alveolar macrophages and transportation to regional lymph nodes where germination occurs. Germination also occurs in the extracellular space of the skin and this process is facilitated by skin defects (e.g. abrasions).

2.3.2. Capsule

The capsule of *B. anthracis* is composed of polymer of D-glutamic acid, which imparts a highly negative charge to the organism. The biosynthetic genes for the capsule are encoded by the pXO-2 plasmid. Similar to the capsule of other microbes, the capsule of *B. anthracis* is believed to contribute to pathogenesis through its inhibitory effects on complement-mediated phagocytosis. Acapsular strains of *B. anthracis* (e.g. Sterne strain) exhibit markedly reduced virulence and are used as vaccine candidates.

2.3.3 Toxins

B. anthracis produces two plasma-encoded proteins**,** lethal factor (LF) and edema factor (EF). These factors combine with another plasmid-encoded protein known as protective antigen (PA) to produce Lethal toxin (LeTx) and Edema toxin (EdTx). PA binds two cell membrane receptors, human tumor endothelium marker-8 and capillary morphogenesis protein 2. PA is named as such because antibodies to this protein can protect against anthrax and PA is the relevant antigen in current vaccine formulations. After receptor binding, the protein is cleaved by a cell-associated furin into two fragments, PA20 and PA63. The PA20 fragment is released from the cell and is not believed to play any additional role in toxin pathogenesis. The PA63 fraction oligomerizes on the cell surface and actively binds lethal factor and edema factor. The resulting complexes are taken up by the cell and eventually enter the cytoplasm where these toxins mediate numerous actions that dysregulate cell function. EdTx is an adenylate cyclase and produces increased levels of cAMP within the cell. LeTx is Zn^{2+}-dependent endoprotease, which cleaves seveal proteins in the mitogen-activated protein kinases (MAPK) pathway. LeTx produces cell death both *in vitro* and *in vivo*, though the role of MAPK inactivation in cell death and clinca shock are not known. The biologic activity of these toxins has been hypothesized to contribute significantly to the manifestations of shock (see below). *B. anthracis* also produces a cholesterol-dependent cytolysin, anthrolysin, which is thought to promote escape of the bacteria from the cellular phagolysosome (2).

3. HUMAN DISEASE

3.1. Clinical Manifestations

The clinical manifestations and mortality of human anthrax depend on the route of inoculation with pulmonary disease producing the highest mortality, followed by gastrointestinal and skin disease. The skin manifestations of anthrax include a papule or vesicle that enlarges and ulcerates leading to the formation of black eschar. Associated symptoms include the following: swelling, regional adenopathy and constitutional symptoms (e.g., fever, malaise and headache). Gastrointestinal anthrax can manifest as oropharyngeal or intestinal disease. Gastrointestinal anthrax typically occurs after ingestion of contaminated and undercooked meats. Affected patients develop symptoms associated with acute inflammation of

the intestinal tract, including the following: nausea, vomiting, fever, ascites, and hematemesis. Patients with oropharyngeal disease develop high fevers with ulcers in the posterior pharynx, neck swelling and regional adenopathy. Pulmonary anthrax often exhibits a biphasic course. Affected patients present with cold and/or flu-like symptoms, including: fever, chills, non-productive cough, myalgias and malaise. Patients then develop mediastinal lymphadenitis and pleural effusions and ultimately develop respiratory distress and shock. Some patients with inhalational anthrax experience a period of symptomatic improvement before the development of shock. Alternatively, patients with pulmonary anthrax may present with shock without early respiratory symptoms (3).

3.2. Sepsis

The manifestations of anthrax-associated sepsis can be present in association with any form of anthrax, though they are more typically associated with pulmonary and gastrointestinal disease. Sepsis is often marked by hi-grade bacteremia, leading early investigators to hypothesize that the high bacterial blood burden was directly responsible for host death through mechanical obstruction of the vascular system. Nonetheless, experiments with toxin and variety of animal models have clearly demonstrated that hi-grade bacteremia is not required for host death. Other features associated with anthrax sepsis include the following: hemorrhage, edema, inflammation and ultimately hemodynamic collapse.

3.3. Hemodynamic Collapse

Cardiovascular collapse producing hypotension occurs in the later stages of anthrax though some patients present with hypotension. Typically, patients have evidence of significant end organ involvement. For patients with inhalational anthrax this includes respiratory insufficiency in association with pulmonary disease. A variety of animal models utilizing infection and intoxication has been used to study *B. anthracis*-induced shock. In these studies, bradycardia, hypotension and EKG abnormalities have been reported (4-8).

3.4. Cardiac Effects

A direct effect of *B. anthracis* infection or toxin on cardiac function has not been definitively established. In a necropsy review of 41 cases of documented inhalational anthrax from the Sverdlovsk epidemic of 1979, Grinberg *et al* documented minimal evidence of direct cardiac involvement. In this regard, only small numbers of *Bacillus anthracis* organisms were identified in cardiac sections of 9 of 25 patients and there were no specific cardiac microscopic findings (9). Pericardial effusion has been reported in association with anthrax, though it does not appear to contribute significantly to the pathophysiology of anthrax- associated shock. In a review of cases related to US mail contamination, 3 of 10 patients developed pericardial effusion, one went on to have tamponade (10).

Animal model studies have also failed to demonstrate significant cardiac pathology associated with *B. anthracis* toxins. Injection of LeTx in mice produced little to no changes in cardiac histology, including: minimal coagulative necrosis, occasional mild cardiac dilatation and fibroblast infiltration of the myocardial interstitium (5;11). In another study, EdTx injection in BALB/c mice produced cardiomyocyte necrosis and interfiber myxoid accumulation. Platelet/fibrin thrombi were found within coronary vessels (12).

Early animal physiology studies from the 1960s typically described alterations in HR and blood pressure in association with toxin injection and experimental anthrax. It is not clear from these reports whether these changes were primary or secondary events. Signs and symptoms were often noted in the context of respiratory failure and important central nervous system effects were hypothesized. Nonetheless, recent studies in the rat suggest that anthrax toxins have direct effects on cardiac function that contribute to the pathogenesis of anthrax. Watson *et al* have shown that LeTx produced increase left ventricular compliance and resulting ventricular dysfunction (13). In this model, EdTx appears to act synergistically with LeTx by causing vascular leakage and reduced ventricular volumes (14;15).

3.5. Bleeding

Hemorrhage into body fluids (e.g. CSF and pleural fluid) and organs (regional lymph nodes, lung, and gastrointestinal tract) is characteristic of anthrax. Frank disseminated intravascular coagulation complicates some cases of anthrax(10;16). In primate and murine model of *B. anthracis* infection, bacteremia produced disseminated intravascular coagulation (4;5). The basis for enhanced bleeding and DIC are not well understood, though an infection-induced vasculitis has been hypothesized to contribute to this process (see below).

3.6. Cytokine Storm

An uncontrolled release of pro-inflammatory cytokines was hypothesized to contribute to the cardiovascular collapse during anthrax in a manner similar to endotoxin-mediated sepsis. Presumably, this relates to macrophage death induced by *B. anthracis* and anthrax toxin with consequent release of pro-inflammatory cytokines. Inflammation as manifested by necrosis and increased peripheral WBC is often present in affected patients and animals models of anthrax. Increased levels of IL-1beta and IL-6 have been found in some, but not all murine strains experimentally infected with *B. anthracis*(17). Likewise, an increase in pro-inflammatory cytokines has been described following intravenous injection of *B. anthracis* in non-human primate model of anthrax (4). LeTx has also been reported to cause a release of IL-1 beta and TNF- alpha by murine macrophages *in vitro* (18-20). A role for cytokine storm in the pathogenesis of anthrax is also supported by the observation that TNF receptor 1, IL-1 receptor and iNOS deficient mice are less susceptible to infection than wild type mice (21). Finally, the importance of macrophage produced cytokines in anthrax pathophysiology is highlighted by murine experiments that document protection from the lethal effects of anthrax by macrophage depletion (18).

The mechanism of cytokine release is uncertain but there is evidence that activation of Toll-like receptors (TLR) may contribute. Incubation of macrophages with *B. anthracis* spores and bacteria resulted in the production of IL-6, TNF-alpha, IL-10, and IL-12 p40 (22). Inhibition of TLR 7 and 9 reduced IL-6 and TNF-alpha secretion and decreased macrophage cytotoxicity (22). The observation that anthrolysin O can be a ligand for TLR4 (23), the same receptor for endotoxin, raises the intriguing possibility that the similarities in the cardiovascular collapse observed in anthrax and gram-negative sepsis share a common mechanistic basis.

Nonetheless, there is conflicting data with respect to the role of inflammation and pro-inflammatory cytokines in the pathogenesis of anthrax. For example, LeTx reportedly produced a transient or negligible increase in pro-inflammatory cytokines in mice and rats, despite its lethal effects (6;11). Furthermore, a lack of cytokine release was reported following low level exposure of macrophages to LeTx (24). In addition, cells treated with sublethal LeTx doses have blunted pro-inflammatory cytokine responses following LPS stimulation (25;26). These findings have led to the hypothesis that low levels of toxin, perhaps found early in the disease have a net anti-inflammatory effect and promote *B. anthracis* survival.

In summary, the role of cytokine dysregulation in the pathogenesis of anthrax-induced shock remains to be fully defined. *In vitro* studies suggest that anthrax toxins (e.g. LeTx, EdTx, and anthrolysin O) play a role in this process, but their effects may be dose and host dependent.

3.7. Vascular Effects

A loss of vascular integrity typically accompanies anthrax and manifests as hemoconcentration and pleural effusions. This loss of vascular integrity is also likely to contribute to the hemodynamic collapse associated with anthrax. Increased vascular permeability can be reproduced in animal models by LeTx injection. It has been suggested that LeTx directly alters vascular permeability, through its effects on the endothelial cytoskeleton, including an increase in central actin stress fibers and significantly altered VE-cadherin distribution (27). LeTx also causes endothelial cell death via apoptosis (28;29). Recently, LeTx was shown to kill mast cells producing histamine release. The same authors reported that intradermal vascular leakage can be inhibited by ketotifen, an inhibitor of mast cell degranulation, though mast cell deficient mice still developed vascular leakage in response to systemic challenge with LeTx suggesting that other factors may be involved in producing systemic vascular leakage (30). EdTx through its effects on cyclic AMP has also been implicated in the alterations in vascular integrity by causing vascular dilatation and producing cytoskeletal changes and inhibits chemotaxis of endothelial cells. Interestingly, fluid resuscitation with normal saline in rats counteracts the beneficial effects of mAb-mediated LTx neutralization (31). This effect may reflect deleterious effects of fluid resuscitation in the setting of impaired vascular integrity.

Vasculitis may also contribute to the alterations in vascular permeability associated with anthrax. A review of the pathologic findings of victims from the accidental release of *B. anthracis* spores in Sverdlovsk revealed a prominent neutrophilic vasculitis involving both arteries and veins along with smaller vessels, which could contribute to enhanced bleeding (9). Vasculitis has also been reported in animal models of anthrax (5;32). Nonetheless, an examination of tissue specimens from victims of the 2001 anthrax attack also found evidence of organ hemorrhage, but failed to identify significant vasculitis (33).

4. THERAPY

The management of anthrax-associated shock and cardiovascular collapse remains dependent on antimicrobial and supportive therapy. However, several agents are being developed that may be useful for specific treatment of this condition. Antibody therapy with LF-specific antibodies consistently reduces mortality in animal models of disease. Although passive antibody administration is usually more effective in preventing disease than in treating disease there are encouraging reports that late administration of PA-neutralizing antibody can improve hemodynamic function in a rat model of anthrax (34). Similarly, a human mAb was protective in rabbits even when administered 3 d after inhalational infection (35). A human antibody to PA has completed Phase 1 testing raising hopes that antibody-based therapeutics may be available for human therapy(36) if we need to confront the calamity of future cases of inhalational anthrax.

5. CONCLUSIONS

In summary, the shock associated with anthrax is associated with an extremely high mortality, despite anti-microbial therapy. The clinical features of this process are similar in some ways to shock induced by other bacterial pathogens, but are also quite distinctive. Clinical studies and animal experimentation support the unique nature of anthrax-associated shock. These studies reveal the role of anthrax toxins in promoting multiple system dysfunction, including the following: inflammation, altered vascular permeability and coagulation disturbances. Many questions remained unanswered and additional study both related to the pathogen and host are needed. An increased understanding of the pathophysiology of this process is essential to the design of new agents that can reduce the high mortality of this disease.

6. ACKNOWLEDGEMENTS

Supported by AI057158 (Northeast Biodefense Center-Lipkin).

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Abbreviations: Protective Antigen (PA), Lethal factor (LF), Edema factor (EF), Lethal toxin (LeTx), Edema Toxin (EdTx)

Key words: Anthrax, shock, Bacillus anthracis, Lethal toxin, Edema toxin, Review

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