REVIEW

Anthrax: a disease in waiting?

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Anthrax was a relatively unknown disease in the Western world until 2001, when spores were maliciously mailed in the US, causing five deaths. The mortality of the disease, the stability of its spores and the subsequent lack of person-to-person spread make anthrax an attractive biological weapon for terrorists with a desire for targeted mass destruction.

Anthrax is an ancient disease that is rarely seen outside well-defined geographical areas, except as an occasional occupational hazard of animal hide handlers.¹ Its current importance is its potential use for bioterrorism. One kilogram of *Bacillus anthracis* spores released over a crowded city of 10 million would cause >100 000 deaths despite antibiotic prophylaxis.² Unlike other unfocused biological weapons such as smallpox or plague (which would spread unpredictably and involve associates of the liberators), anthrax does not spread from person to person and thus only the area that is attacked would effectively be made uninhabitable.

PATHOGENESIS

Anthrax is a disease of herbivores, especially ruminants. Humans are infected by contact with infected animals or by contact with animal products.¹ Anthrax is initiated by spores that enter via small abrasions, or by inhalation or ingestion.³ These hardy spores are resistant to drying, heat, ultraviolet light, γ -radiation and many disinfectants.⁴ In 1942, spores released experimentally on Gruinard Island, off the west coast of Scotland, persisted for 48 years⁴ and decontamination required 280 tons of formaldehyde and the removal of top soil.⁵ The final report at that time suggested that anthrax could be used to render cities uninhabitable “for generations”.⁶

After entering into the body, spores are carried by phagocytes to regional lymph nodes where they can become dormant, enter a vegetative state or enter the bloodstream.⁷ Vegetative bacteria secrete two exotoxins: oedema toxin and lethal toxin. Oedema toxin causes swelling of the affected areas by altering cellular cyclic AMP levels. Lethal toxin is responsible for evoking the release of tumour necrosis factor α and interleukin 1 by macrophages, and it is linked to shock and sudden death.⁸ Even if sterility of the bloodstream is maintained by antibiotics, high levels of lethal toxin can cause death.⁵

BIOWEAPON POTENTIAL

The high death rate, spore persistence and restriction of infection to those exposed to it make anthrax an attractive bioweapon. The US military ran a biological weapon programme including anthrax until 1969.⁴ Accidental release of spores occurred in Sverdlosk in Russia in 1979.⁹ In September 2001, envelopes containing bioengineered *B anthracis* spores were mailed to several locations in the US.¹⁰ Eleven patients had cutaneous anthrax and of the eleven with inhalation anthrax, five died. Postal workers handling envelopes were probably infected via the airborne

route. Four of those infected, who did not handle infected letters and had never been to buildings where infected letters were handled, presumably were infected by cross-contamination. Overall, prophylaxis was offered to >10 000 people, including all postal workers in Washington, DC.¹¹ Although adherence was poor (44%), no additional cases were reported.¹²

CLINICAL FEATURES

Anthrax occurs in three forms depending on where spores arrive.

Cutaneous anthrax occurs in 95% of natural infections and is generally an occupational disease of farmers (fig 1), butchers, veterinarians and people processing animal products including wool, bones and hides.³ Once spores enter abrasions, a pruritic papule resembling an insect bite appears within 2–7 days. The papule then enlarges and develops vesicular elements (fig 2). The rupture of vesicles occurs on days 5–7 with an eschar and much surrounding oedema.^{1–13} Symptoms such as eschar with oedema, painless lesions and lack of pus may help to differentiate it from other diseases (table 1). Skin manifestations usually resolve slowly within 6 weeks, but a small proportion of the untreated patient may progress to systemic anthrax.^{1–8}

Gastrointestinal disease can develop if spores are ingested. Acute abdominal symptoms, including haematemesis, bloody diarrhoea and massive ascites may develop, mimicking food poisoning in the early stages and necrotising enteritis in severe cases.¹ The prognosis for gastrointestinal disease is poor, with septicæmia and shock.⁸

Inhalation Anthrax is caused by spore inhalation. It is not a true pneumonia, as inhaled spores are transported to mediastinal lymph nodes to initiate haemorrhagic mediastinitis.⁸ A diagnosis of inhalation anthrax should raise the probability of a biological attack. The usual incubation period is 1–7 days, but spores can germinate much later than this—6 weeks in the Sverdlosk outbreak.⁹ The symptoms include

Figure 1 Hand affected with *Cutaneous* anthrax (kindly supplied by Prof M Doganay, Kayseri Turkey).

Figure 2 Enlarged papule with formation of vesicular elements (kindly supplied by Prof M Doganay, Kayseri, Turkey).

rapid-onset fever, chills, sweating, fatigue, minimally productive cough, nausea or vomiting and chest discomfort.¹⁰ The initial clinical presentation with non-specific symptoms is similar to atypical pneumonia. Sore throat and rhinorrhoea are unusual and might help to differentiate inhalation anthrax from viral respiratory illnesses. Initial chest x-rays show mediastinal widening, pleural effusion or pulmonary infiltrates.⁵ The disease progresses to the second stage in 2–3 days with further fever, dyspnoea, cyanosis and shock. In 2001, the death rate of inhalation anthrax cases was 45%, compared with 86% in the earlier Sverdlosk outbreak.^{9 10} This improvement might be related to the administration of more antibiotics, better supportive care and differences in host

susceptibility.^{5 14} Patients with inhalation or systemic anthrax usually die rapidly, often before a definitive diagnosis can be made.

DIAGNOSIS

B anthracis is easily isolated from blood cultures in <24 h.⁷ Swabs from a cutaneous lesion may be positive.¹ Gram stains of peripheral blood, pleural effusion, ascites and cerebrospinal fluid (if meningitis is suspected) can disclose bacilli.³ Polymerase chain reaction of blood and sterile body fluids helps to diagnose patients who have received antibiotics.^{5 8}

MANAGEMENT

B anthracis is susceptible to penicillin but given the possibility of bioengineered strains as seen in the US, parenteral ciprofloxacin or doxycycline in combination with another antibiotic is recommended.^{5 14}

The duration of therapeutic or prophylactic treatment for inhalation anthrax is uncertain. Sixty days is recommended because spores can germinate weeks after inhalation.^{8 14} A vaccine is available for use in military settings.¹

CONCLUSION

In the absence of a mass outbreak, most patients with cutaneous anthrax will be diagnosed because of occupational exposure. The early recognition of cutaneous anthrax by general practitioners will be pivotal and provide a diagnostic clue to other patients presenting with severe respiratory illnesses whose diagnosis might otherwise have to await postmortem examination. Prompt treatment and post-exposure prophylaxis will be essential.

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Table 1 Differential diagnosis^{1 3 8}

Clinical form	Differential diagnosis	Diagnostic clues for anthrax
Cutaneous anthrax	Insect bite	Occupational history Eschar with oedema Anthrax lesion is painless No pus unless secondary infection Swabs from vesicular lesions showed Gram-positive encapsulated rods
	Staphylococcal skin disease	
	Orf	
	Erysipelas	
	Ecthyma gangrenosum	
	Tularaemia	
	Plague	
	Syphilitic chancre	
	Tropical ulcer	
	Necrotising soft tissue infection	
	Cutaneous tuberculosis	
Gastrointestinal anthrax	Food poisoning	History of contaminated meat ingestion Gram stain of faecal and vomit specimens Ascetic Gram stain and culture Blood culture
	Acute gastroenteritis	
	Acute abdomen	
	Necrotising enterocolitis	
Inhalation anthrax	Viral respiratory illness	History of occupational or accidental exposure x Ray: mediastinal widening pleural effusion Pleural fluid Gram stain, culture and PCR Blood culture
	Atypical pneumonia	
	Plague	
	Tularaemia	
	Histoplasmosis	
	Cardiovascular collapse (eg, ruptured aortic aneurysm)	
Anthrax meningitis	Bacterial meningitis	Haemorrhagic spinal fluid CSF examination, Gram stain, culture, PCR Blood culture
	Subarachnoidal haemorrhage	
	Herpetic meningoencephalitis	

CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

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