Acta Med. Okayama, 2003
Vol. 57, No. 5, pp. 235-240
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Acta Medica Okayama
http://www.lib.okayama-u.ac.jp/www/acta/

Original Article

Cutaneous Manifestations of Anthrax in Eastern Anatolia: A Review of 39 Cases

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Anthrax is essentially a disease of grazing herbivorous animals. The most common form of the disease is cutaneous anthrax, which accounts for 95% of all cases. We report here 39 cutaneous anthrax cases in humans that were seen in Eastern Anatolia over a six-year period. The clinical presentation was malignant edema in 16 of the cases (41%) and malignant pustule in 23 (59%). A secondary bacterial infection was present in 13 patients (33.3%) in the vicinity of the lesions. The agent was observed using Gram-stained smears in 25 patients (64%), and *Bacillus anthracis* was isolated from 15 patients (38.5%). All of the patients were treated with penicillin G or penicillin procaine, except one patient who had a penicillin allergy. One patient with cervical edema (2.5%) died as a result of laryngeal edema and sepsis syndrome. In conclusion, we found that the appearance of the skin lesion of cutaneous anthrax may vary, and this fact, combined with the rarity of this disease, which contributes to a general lack of experience among medical personnel, may make diagnosis difficult in nonagricultural settings.

Key words: cutaneous anthrax, clinical findings, treatment, prognosis

Anthrax is essentially a disease of grazing herbivorous animals. The causative organism is *Bacillus anthracis*, a Gram-positive, non-motile, aerobic, spore-forming, rod shaped bacterium that forms a large polypeptide capsule detectable in clinical specimens [1-3]. *B. anthracis* produces an antigenic exotoxin that is believed to be responsible for many of the clinical symptoms of anthrax. The toxin is tripartite, consisting of an edema factor, a lethal factor, and a protective antigen [4-8].

Anthrax cases in humans may be classified as industrial or agricultural according to the spread route [2]. The disease can clinically present in a cutaneous, gastrointestinal or inhalational form depending on the entry site of the agent. Under natural conditions, humans become infected with anthrax (usually the cutaneous form) due to contact with infected animals or contaminated animal products, such as hides, wool, hair, and bone and bone products. Exposure also may result from a bioterrorist act (*e.g.* a contaminated letter). In rare cases, gastrointestinal (or oropharyngeal) anthrax has appeared after the ingestion of poorly cooked endospore-contaminated meat. Cases of inhalational anthrax (also known as woolsorters' disease) have been linked to the large-scale processing of hides and wool in enclosed factory spaces, where aerosolized anthrax spores may be inhaled [9-11].

Cutaneous anthrax, when treated, rarely leads to sepsis and meningitis in contrast with the other forms of

Received Junuary 7, 2003; accepted March 24, 2003.
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anthrax which may give rise to death. In cutaneous anthrax, the organism's portal of entry is a cut or abrasion on the skin. The areas of greatest exposure are the hands, arms, face and neck. The skin infection begins as a raised pruritic papule, resembling an insect bite. A vesicle develops within 1–2 days, followed by a painless ulcer 1–3 cm in diameter with a characteristic black necrotic eschar in the center. Localized lymphangitis and painful lymphadenopathy may occur. Although antibiotic therapy does not appear to change the course of eschar formation and healing, it does decrease the risk of systemic disease [12].

Because preventive health measures in workplaces, anthrax is rare in developed countries, but it is common in developing countries in Asia Minor, particularly Iran and Turkey. Between 20,000 and 100,000 cases of anthrax have been estimated to occur annually worldwide, but in the United States, the annual incidence over the 20 years prior to September 2001 was less than 1 case per year [13, 14].

Cases of cutaneous anthrax and cases of illness associated with anthrax complications in different regions of Turkey have been previously reported [15–17]. The aim of our study is to evaluate the types of anthrax cases that are encountered frequently in the Van region of Eastern Anatolia with respect to clinical features, treatment and prognosis.

Materials and Methods

This study includes 39 patients diagnosed with and treated for cutaneous anthrax in the Van region. All of the patients were admitted to Yüzüncü Yıl University, Medical School Hospital, between March 1996 and March 2002. The diagnosis was based on clinical and microbiological findings. Routine blood analysis, peripheral blood smear, ESR, and blood culture analysis were performed in all patients. The microbiological examinations included Gram staining of the materials taken from the lesions as well as direct examination and culture methods. Sheep's-blood agar was used, and large nonhemolytic white-gray colonies with irregularly tapered outgrowths (a medusa's head appearance) were evaluated. Gram-stained smears from the culture showed rod-shaped bacteria growing as long chains. A Gram-positive breakpoint ID panel (Becton Dickinson Diagnostic Instrument Systems) was used in the identification.

Results

The study included 39 patients between 5 and 65 years old (mean age, 34), 25 of whom were females (64%) and 14 of whom were males (36%). The disease was seen in all age groups, but there was a gender difference which resulted from the fact that in this region women mainly deal with animal husbandry (Table 1).

The distribution of the cases according to their professions is shown in Table 2. Seventeen of the cases were from a city center, and 22 were from counties or villages. The distribution of the appearance of the cases did not differ by year but showed a density in the months from July to October.

All patients showed a history of bringing up sheep or cattle and slaughtering or processing them—*i.e.*, skinning or cutting meat from an animal alleged to have shown symptoms of anthrax—or eating contaminated meat. Since the contact with animals was long-lasting in all of the patients, the incubation period of the disease was not objectively determined.

All of the cases were in cutaneous form, and the clinical presentation was malignant edema in 16 of them

Table 1 Age and gender distribution of the cases

Age	Female	Male	Total
≤20	3	4	7
21–30	6	2	8
31–40	6	4	10
41–50	7	2	9
51–60	3	1	4
>60	–	1	1
Total	25 (64%)	14 (36%)	39 (100%)

Table 2 Profession distribution of the cases

Professions	Case number
Husbandry	14 (35.9%)
Farmer	9 (23 %)
Butcher	4 (10 %)
Shepherd	3 (7.7%)
Craftsman	2 (5 %)
Child	5 (12.8%)
Student	2 (5 %)
Total	39 (100 %)

(41%) and malignant pustule in 23 (59%). Lesions on the face and neck were in the form of malignant edema (Figs. 1, 2), and lesions on the hand and arms were in the form of malignant pustule (Figs. 3, 4). The distribution of the lesions by localization site is shown in Table 3. A secondary infection with another bacterial agent was present in the vicinity of the lesions in 13 patients (33.3 %). Following medical treatment, reconstructive surgery was performed in 5 patients with scar lesions on the

Table 3 Localization sites of the lesions

Localization site	Case number
Hands and fingers	15 (38.5%)
Arms	8 (20.5%)
Eyelids	10 (25.6%)
Lips and surrounding area	3 (7.7%)
Neck	3 (7.7%)
Total	39 (100 %)

Fig. 1 Extensive edema surrounding the left eye and on the left submandibular region and necrotic ulcer and hyperemia on the lower eyelid.

Fig. 2 A black necrotic central eschar surrounded by hyperemia on the lower eyelid. (This figure shows the same patient shown in Fig. 1 after recovery.)

Fig. 3 Necrotic lesions surrounded by hyperemia on the dorsal surfaces of the thumb and ring finger of the left hand (from various aspects).

Fig. 4 A necrotic lesion with extensive edema on the dorsal face of the right wrist.

eyelids, 3 patients with lesions on the right hand, and 1 patient with a lesion on the right arm, for a total of 9 patients (23%).

The agent was observed through direct examination of Gram-stained smears in 25 patients (64%). *Bacillus anthracis* was isolated from vesicle fluid cultures in 15 patients (38.5%). Twelve patients (30.8%) had received an antibiotic before admission to our clinic. Serological tests could not be conducted.

In the treatment of the malignant pustules, procaine penicillin was used (800,000 units IM every 12 h in adults and 400,000 units IM every 12 h in children) for one week. The treatment was started with penicillin G (2–3 million units every 4 h in adults and 500,000 U/kg/day in children) in the cases with malignant edema presentation. After about 3 days, the treatment was changed to procaine penicillin and continued through the tenth day. Systemic corticosteroids were added to the antibiotic treatment in 13 patients (33.3%) with the malignant edema form. For this purpose, prednisolone (1–2 mg/kg/day) was used for 3 days. In addition, the lesions were topically covered with gauze embedded with rivanol. Erythromycin was replaced in 1 patient with the malignant pustule presentation because of a penicillin allergy. Ciprofloxacin was added to the standard therapy in 13 patients (33.3%) having a secondary infection with staphylococci or streptococci. The mean hospitalization duration was 7 days in cases with the malignant pustule presentation and 13 days in cases with the malignant edema presentation. One patient with cervical edema (2.5%) died as a result of laryngeal edema and sepsis syndrome.

Discussion

Anthrax continues to be an important infectious disease among herbivorous animals such as sheep and cattle, especially in developing countries. The regions with widespread infection include all African countries, Russia and the Turkey-Iran-Pakistan crescent [18].

The most important means of subsistence for the population in our region, not only in villages but also in rural areas and even city centers, is animal husbandry, which is being performed by traditional methods. Animal anthrax increases in arid seasons in these countries in which anthrax is present [19]. This explains the increase in human anthrax cases in the same season in our region.

Not all of the anthrax cases that occur in our region are referred to our clinic, with some cases, especially those presenting in malignant pustule form, being treated in first-step health care facilities. Therefore, we consider the incidence of anthrax in our region to be much higher than our own caseload suggests.

Although anthrax has been reported to be seen more frequently in men rather than women in some series, Kaya *et al*. [16] and Doğanay *et al*. [17] have observed no gender difference in the disease in their reported series. In the present study, however, we detected a significant difference in gender. Females constituted 65.4% of our cases as shown in Table 1. This finding reveals that, in rural areas, women deal with animal husbandry instead of or at least as much as men.

Whereas industrial cases account for most of the anthrax cases in developed countries in which there is no conventional exposure to infected animals or animal products, the spread of anthrax in developing countries occurs most frequently by direct contact [17]. We found that in all of our cases the anthrax was contracted by direct contact.

Cutaneous anthrax accounts for more than 95% of all clinical forms of anthrax throughout the world [2, 20]. This rate was 100% in our series, which correlates with the rate in the series reported by Kaya *et al*. [16]. The clinical prognosis was more severe in cases with facial and cervical localization, and the hospitalization period in these cases was above the average.

Diagnosis is achieved by detecting the agent in Gram-staining of the vesicle fluid and/or detecting the growth of the microorganism in the culture [21]. In addition, ELISA and EITB (Enzyme-linked immune-electro-transfer blotting) methods have been used for antibody detection [22, 23]. Plague, tularemia, glanders, ecthyma gangrenosum, ulcerative skin lesions, rickettsial pox, rat-bite fever, orf, staphylococcal lymphadenitis, cutaneous tuberculosis, leprosy, and Buruli ulcer must be considered as differential diagnoses of cutaneous anthrax [24].

In 64% of our cases, the agent was able to be revealed by direct examination of Gram-stained smears and/or by culture methods. The fact that the causative agent could not be detected by microbiological methods in 36% of all cases can be explained by the use of antibiotics by some patients (30.8%) before their admission to our clinic. As a matter of fact, cultures taken from the lesions of patients who were treated with penicillin have become negative within a few hours after the initiation of the

therapy [2]. Therefore, we can conclude that the diagnosis may clinically be achieved in patients with the proper history and physical examination findings. Penicillin has been the drug of choice for anthrax for many decades, and only very rarely has penicillin resistance been found in naturally occurring isolates. Other antimicrobial drugs commonly used in the treatment of anthrax include the quinolones, tetracyclines, chloramphenicol, aminoglycosides, and the first-generation cephalosporins that have also been encountered in our antibiotic susceptibility testing [10, 25–28].

Penicillin G was used and found to be effective in all of our cases except one, in whom erythromycin was used because of a penicillin allergy. The death of 1 patient due to laryngeal edema alerted us to be conscious of respiratory problems that may be encountered, especially in the malignant edema presentation of the disease. Controlling cutaneous anthrax cases in humans depends on controlling the disease in herbivorous animals. Animals that die of anthrax should be buried deeply or incinerated. The vaccination of livestock is effective in eradicating the disease in animals but must be repeated every year. All persons who may be exposed to contaminated materials or a contaminated environment should be vaccinated with a vaccine prepared from the protective antigen. In industrial countries, anthrax has been virtually eradicated because of effective public health measures such as animal vaccination and procedures for decontaminating animal products [5, 9, 29].

In conclusion, *Bacillus anthracis* is the major terrorist and biological warfare agent of concern to civilian and military medical planners [30]. Cutaneous anthrax is the most common form of human infection with this organism. Anthrax spores delivered by aerosol cause inhalational anthrax, an almost uniformly fatal and extraordinarily rare natural presentation of the disease. Because the incubation period of inhalational anthrax may last a few days, the impact of a bioterrorist anthrax exposure could be reduced by early diagnosis; therefore, this disease should be considered as a differential diagnosis for cutaneous anthrax in the case of an unusual epidemic of the cutaneous variety [2]. The appearance of the skin lesion of cutaneous anthrax may vary, and this fact, combined with the rarity of this disease, which contributes to a general lack of experience among medical personnel, may make diagnosis difficult in nonagricultural settings [5].

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