Cutaneous Anthrax in the Central Anatolia Region of Turkey: A Review of 39 Adults Cases

Türkiye'de İç Anadolu Bölgesi'nde Deri Şarbonu: 39 Erişkin Olgunun İrdelenmesi

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ABSTRACT Objective: Anthrax is a zoonotic infectious disease that caused by *Bacillus anthracis*. Sporadic anthrax is still present world-wide, particularly in animal raising countries including Turkey. The aim of this study was to evaluate the epidemiological, clinical, and laboratory findings and treatment protocols of adult patients with cutaneous anthrax retrospectively. **Material and Methods:** A retrospective review of 39 adult patients with cutaneous anthrax presented between 1983 and 2005, in Cumhuriyet University Hospital in Sivas, a city located in the central Anatolia region of Turkey was carried out. **Results:** Of the 39 cases with the diagnosis of cutaneous anthrax, 27 (69.2%) were males and 12 (30.8%) were females. The mean age was 44 (range, 16-74) years. The clinical presentations were severe edema due to anthrax in 10 (26%) and typical pustuler lesion in 29 (74%) patients. The lesions were mostly located on the hand and forearm. Twenty-five cases (64.1%) had a history of recent animal slaughtering activity. Culturing of 39 wound specimens yielded 17 (43.6%) *B. anthracis* strains. Thirty-six (92.3%) patients were treated with penicillin G. A patient with severe cutaneous anthrax and extensive edema died on the first admission day. Mortality rate was 2.6%. **Conclusion:** Although the incidence of anthrax is decreasing world-wide, it is still encountered in Turkey. Preventive measures such as education of the risk population and vaccinaton of animals against anthrax would reduce the incidence of the disease. We suppose that penicillin is still the antibiotic of choice for the treatment of cutaneous anthrax in endemic regions.

Key Words: Anthrax; clinical trial; therapy; Turkey

ÖZET Amaç: Şarbon, *Bacillus anthracis* ile oluşturulan zoonotik bir infeksiyon hastalığıdır. Sporadik şarbon özelikle Türkiye gibi hayvan yetiştiren ülkeler olmak üzere tüm dünyada hala görülmektedir. Bu çalışmada deri şarbonu olan erişkin hastaların epidemiyolojik, klinik ve laboratuvar özellikleri ile tedavi protokollerinin geriye dönük olarak değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmada 1983 ile 2005 yılları arasında ülkemiz İç Anadolu Bölgesi'ndeki Sivas Cumhuriyet Üniversitesi Hastanesi'ne yatırılarak izlenen 39 erişkin deri şarbonu tanılı hastaya ait kayıtlar geriye dönük olarak incelenmiştir. **Bulgular:** Deri şarbonu tanısı alan 39 hastadan 27 (%69.2)'si erkek, 12 (%30.8)'si kadın idi. Ortalama yaş 44 (sınırlar, 16-74) yıl idi. On (%26) hastada klinik görünüm şarbon ödemi, 29 (%74)'unda ise tipik püstüler şarbon lezyonu formundaydı. Lezyonlar en çok el ve önkolda yer almaktaydı. Yirmibeş (%64.1) hastada yakın zamanda hasta bir hayvanı kesme öyküsü mevcuttu. Otuzdokuz hastaya ait yara yeri kültürünün 17 (%43.6)'sinde *B. anthracis* üredi. Otuzaltı (%92.3) hasta penisilin G ile tedavi edildi. Deri lezyonuna bağlı şiddetli hastalık klinik tablosu ve yaygın ödemi olan bir hasta hastaneye yattığı gün öldü. Olgulardaki mortalite oranı %2.6 idi. **Sonuç:** Dünyada giderek azalan şarbon olguları Türkiye'de halen görülmektedir. Risk grubunda yer alan kişilerin eğitilmesi ve hayvanların şarbona karşı aşılanması gibi koruyucu önlemler hastalığın görülme sıklığını azaltabilecektir. Endemik bölgelerde deri şarbonu olgularının tedavisinde penisilinin halen tercih edilebilecek bir antibiyotik olduğunu düşünmekteyiz.

Anahtar Kelimeler: Şarbon; klinik çalışma; tedavi; Türkiye

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Bacillus anthracis, the etiological agent of anthrax, is a Gram positive, aerobic or facultatively anaerobic, spore-forming, rod-shaped bacterium.[1] Anthrax is primarily a disease of herbivores. Humans become accidentally infected through contact with infected animals or their products. Direct exposure to infected animals or animal products through skin exposure, ingestion of undercooked meat, or inhalation of spore-containing particles may be the cause of transmission to humans.[2]

Although inhalational and gastrointestinal forms of anthrax exist, cutaneous infections account for 95% of all anthrax cases.[3] Sporadic cases and outbreaks of naturally-occurring anthrax are still present world-wide although they are relatively rare in developed countries. Anthrax has been estimated to occur worldwide annually with an incidence between 20,000 and 100,000 cases.[4] Epizootic anthrax cases can be find in highly endemic areas, such as Iran, Iraq, Turkey, Pakistan, and Africa, where the use of animal anthrax vaccine is not comprehensive.[2,5,6] Anthrax is an endemic infectious disease in Turkey, and 6730 human anthrax cases were reported between 1990-2006 by the Turkish Minsitry of Health (www.saglik.gov.tr).

In this study, the epidemiological characteristics, clinical and laboratory features, management, and outcomes of 39 patients with the diagnosis of cutaneous anthrax were retrospectively reviewed in an endemic area in Sivas, a central Anatolia city.

MATERIAL AND METHODS

We carried out a retrospective review of 39 patients suspected of having cutaneous anthrax presented between 1983 and 2005, and hospitalized in Infectious Diseases and Clinical Microbiology Clinic of Cumhuriyet University Hospital, an 800 bed-teaching hospital, in Sivas city located in the central Anatolia.

Charts of all hospitalized patients were reviewed for age, sex, occupation, exposure to a sick animal or animal products, symptoms, location and type of lesion, treatment choices and outcomes, and results of routine clinical laboratory tests including complete blood count (CBC), blood biochemistry, erythrocyte sedimentation rate (ESR), Gram stain of lesional swab and both wound and blood cultures, and results were recorded for each patient.

In the vesicular stage, culture material was obtained with needle aspiration. During the eschar stage, it was obtained with sterile swab under an eschar. Obtained specimens were cultured on the sheep blood agar and incubated for 24 hours at 37°C under aerobic conditions. *B. anthracis* isolation was achieved with classical culture method.[1,7] After incubation, non hemolytic, fairly flat, 2-7 mm diametered, white or grey-white colonies with irregular edges were subjected to a further isolation procedure. Gram stained smears from the culture showed Gram positive bamboo-type rods.[1] For the identification of the isolates, cultures were inserted into a semi-solid vertical gelous agar. Characteristic inverted 'fir or pine tree' appearance after incubation for 48 hour at 37°C, lack of mobility in motility agar and catalase positivity established the identification of the isolate.[7,8]

We utilized standardized case classification criteria for our cases as either suspected or confirmed, based on laboratory confirmation according to the World Health Organization (WHO) guideline.[3]

Consent forms were obtained from two patients whose figures were demonstrated. Approval for this retrospective study was obtained from the Human Ethics Committee of Cumhuriyet University School of Medicine.

RESULTS

Of the 39 cases with the diagnosis of cutaneous anthrax, 27 (69.2%) were males and 12 (30.8%) were females, and all patients were from the central and rural areas of Sivas. The mean age of the patients was 44 (range, 16-74) years. Most cases (67%) admitted to the hospital between July and September. Some demographics and risk factors are given in Table 1. Four of the cases included in this study were butchers. Twenty-five cases including butchers (64.1%) had a history of slaughtering activity. Clinical, laboratory and treatment data of the cases are summarized in Table 2. The most common symptoms and signs were erythema, swelling and black eschar in all patients, while

TABLE 1: Demographic data for 39 cutaneous anthrax cases.

Mean age, y (range)	44 (16-74)
Age distribution, n (%)	
16-19 years	4 (10.3)
20-29 years	3 (7.7)
30-39 years	8 (20.5)
40-49 years	5 (12.8)
≥ 50 years	19 (48.7)
Gender, n (%)	
Male	27 (69.2)
Female	12 (31.8)
Occupation, n (%)	
Farmer	23 (59)
Housewife	12 (30.8)
Butcher	4 (10.2)
Risk factors, n (%)	
Slaughtering of a sick animal	25 (64.1)
Family member with anthrax	3 (7.7)
Undetermined	11 (28.2)

hand was the most commonly involved area. The clinical presentation was a cutaneous lesion and extensive anthrax edema (Figure 1) in 10 (26%) and pustuler lesion (Figure 2) in 29 (74%) of the cases. According to the WHO guideline, the number of confirmed and suspected cases were 17 (43.6%) and 22 (56.4%), respectively.

The patients were treated with antibiotics suitable for their clinical conditions. Twenty-five severe form cutaneous anthrax cases received crystallized penicillin G (20 million IU/d) intravenously for seven days. Eleven patients with mild disease received procaine penicillin G (800.000 IU b.i.d) intramuscularly for five to seven days. Three patients with a history of penicillin allergy were treated with intravenous chloramphenicol, oral ciprofloxacin and doxycycline as monotherapy. Systemic corticosteroids were added to the antibiotic treatment in three patients for the managment of extensive edema of anthrax. A severe, septic form of anthrax patient with anthrax edema and cardiac failure died just after admission. Mortality rate was 2.6% among 39 patients. Complications included cicatricial ectropion of the upper eyelid in one patient, and abnormal scar formation on the arm in another patient; all the other cases recovered without any complications or sequela.

DİSCUSSION

Although the incidence of anthrax has decreased dramatically in developed countries, it is still a common infectious disease in many developing countries where animals are raised with traditional techniques. Anthrax has gained more attention recently because of its potential use in biologic warfare such as anthrax cases of Sverdlovsk and the

TABLE 2: Symptoms, signs and laboratory findings on admission and treatment data for 39 cutaneous anthrax cases.

Variable, n (%)	
Symptoms and signs	
Swelling	39 (100)
Erythema	39 (100)
Black eschar	39 (100)
Vesicle	20 (51.3)
Pruritus	30 (76.9)
Regional lymphadenopathy	11 (28.3)
Fever [a]	19 (48.7)
Pain	5 (12.8)
Dyspnea	3 (7.6)
Lesion location	
Hand	19 (48.7)
Arm	9 (23.1)
Face	11 (28.2)
Eyelid	8 (20.5)
Around lips	3 (7.6)
Laboratory findings	
Positive Gram stain	8 (20.5)
Isolation of B. anthracis (wound)	17 (43.6)
Elevated ESR[b]	9 (23.1)
CRP (>5 mg/L)[c]	8 (20.5)
Leucocytosis (>10.000/mm3)	18 (46.1)
Leucopenia (<4000/mm3)	3 (7.7)
Treatment	
Crystallized penicillin G	25 (64.1)
Procaine penicillin G	11 (28.1)
Ciprofloxacin	1 (2.6)
Chloramphenicol	1 (2.6)
Doxycycline	1 (2.6)

[a] Arm pit, ≥38°C.
[b] ESR, erythrocyte sedimentation rate (female ⑧20 mm/hr, male ⑧15 mm/hr).
[c] CRP, C-reactive protein.

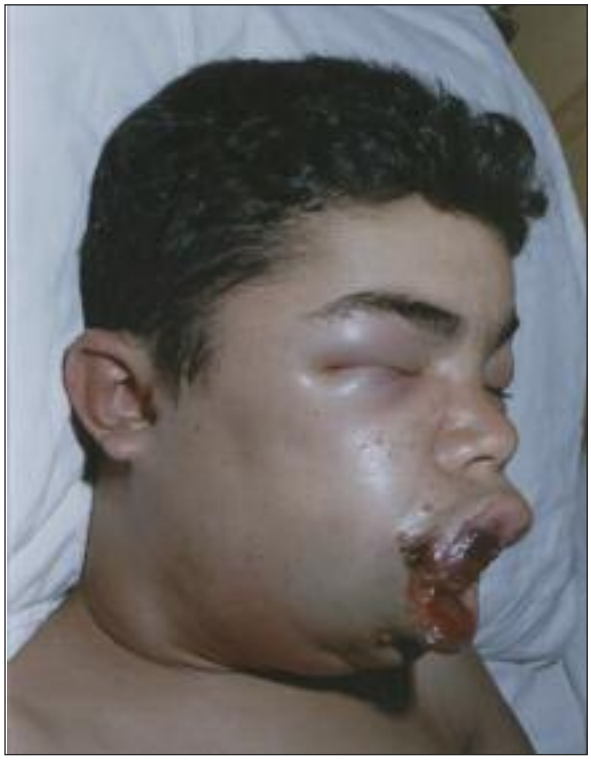

FIGURE 1: Cutaneous anthrax lesion on lips with extensive edema on the face accompanied by regional lymphadenopathy and swallowing difficulty.

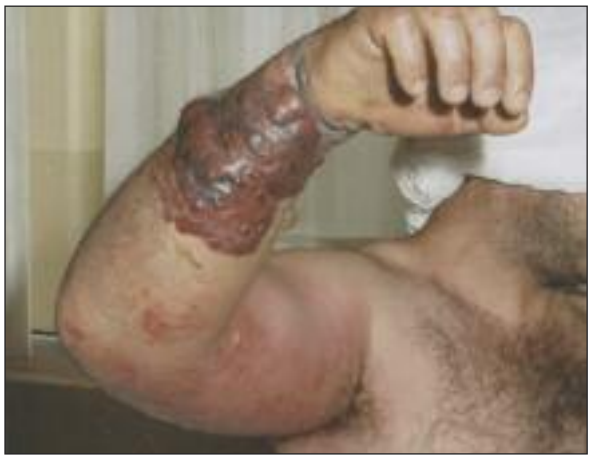

FIGURE 2: Hemorrhagic bullae on the right arm and redness and extensive swelling until the sholder in a butcher. Appearence of a typical severe cutaneous anthrax lesion.

United States.[9,10] In spite of the fact that the disease can occur in three major clinical forms (cutaneous, gastrointestinal, and inhalational), approximately 95% of all human anthrax cases is cutaneous anthrax.[3] A few cases of gastrointestinal anthrax have been reported, but inhalation anthrax has not yet been reported in Turkey.[11-14] Almost all reported cases in Turkey were cutaneous anthrax.[6,15-20] Similarly, all of our cases were in cutaneous form, however, six gastrointestinal anthrax cases in Sivas during the same period were reported.[12]

In addition to the clinical classification, anthrax may be classified as industrial or agricultural according to the route of exposure. Agricultural cases result from the ingestion of undercooked meat or direct contact with infected or died animals that are sick or have died from anthrax. Examples of industrial contact include exposure to anthrax spores that contaminate raw materials, such as hides of infected animals, or wool or bones that are used as part of a manufacturing process. While industrial cases are associated with industrialized countries,[4] agricultural cases are the dominant form of infection in developing countries such as Turkey.[15] Except for one study,[21] all reported cases from Turkey were agricultural anthrax cases,[6,16-19,22] and all of our cases were also agricultural anthrax.

Although no gender difference was reported in some studies,[11,15,17-19] males constituted 69.2% of our cases. This may be due to male predominance as a worker in animal husbandry in our region. Indeed, almost all of our cases had been working for animal husbandry and twenty-five (64.1%) cases had a history of sick animal slaughtering activity in recent times. Irmak et al. have reported female preponderance and suggested that in rural areas, women deal with animal husbandry instead of\ or at least as much as men.[6] These two different results for gender prevalence in the same country may be due to regional occupational differences between males and females.

The most common location of the cutaneous anthrax in the literature is upper limbs,[15-20,23,24] as in our study. This could be due to trauma to the hand and the forearm as a result of working with infected animals. Cutaneous anthrax is seen in two clinical forms; severe cutaneous lesion with extensive edema presenting with systemic symtoms, and mild cutaneous anthrax characterized with typical pustuler lesions presenting with no systemic

symptoms or mild symptoms. In our study, the clinical presentation was severe cutaneous anthrax and extensive edema in 10 (25.6%) cases and mild cutaneous anthrax with typical pustuler lesion in 29 (74.4%) cases. This was consistent with the lesion location. Lesions on the face were in the severe form with extensive edema because of soft tissue characteristics, and lesions on the hand and arms were in the mild form with a pustuler lesion. In the present study, about half of the patients had a high grade of fever. Fever was found in 69% and 81% of the patients in other studies.[15,23] These findings suggest that fever is common in uncomplicated cutaneous anthrax even in a localized infection.

An enzyme-linked immunosorbent assay (ELISA) for immunoglobulin G antibodies against *B. anthracis* protective antigen (PA) in human serum is useful for diagnostic purposes.[25] Because acute and convalescent serum samples are needed, serologic diagnosis is generally useful for retrospective diagnosis.[26] The newest diagnostic modality is a polymerase chain reaction (PCR).[25] Currently, however, PCR and serology have been studied in a limited number of cases in the specific laboratories. Practically, diagnosis of cutaneous anthrax is achieved by detecting the agent in Gram staining of the lesion or detecting the growth of the microorganism in the culture when a typical clinical lesion is present. Although we obtained culture specimen before antibiotic therapy, culture positivity was 43.6% in our study. Wound culture positivity has been reported between 12.9-44%.[15,17-19] The rate of positive anthrax cultures from skin lesions does not exceed 60–65%, probably due to the prior use of antimicrobial therapy or due to the microbicidal activity of local antagonistic skin flora.[27]

In this study, by using the WHO guideline,[3] seventeen cases were classified as confirmed cases with the typical clinical findings for cutaneous anthrax, history of exposure to animal products, and positive cultures from the lesions for *B anthracis*. Eight cases having lesions resembling cutaneous anthrax, history of exposure to infected animals and the presence of Gram positive bacilli giving a bamboo appearance in their lesional smears were included in suspected cases. The diagnosis was established by consistent history and typical clinical presentation in the remaining 14 (35.9%) cases. These 14 cases were also classified as suspected cases.

Despite various antibiotics were used in the past, penicillin is still the first optional drug in the treatment of anthrax.[15,28-31] Almost all isolates of *B. anthracis* can be expected to be highly sensitive to penicillin and, being cheap and readily available in most parts of the world, penicillin remains the basis of treatment schedules, particularly in animals and in humans in developing countries.[3] However, there are few reports of clinical isolates in the literature that are resistant to penicillin.[32,33] Penicillin resistance in anthrax still has not been reported in Turkey.[31] Majority of our cases (92.3%) were treated with either intravenous or intramuscular penicillin G in this study. Except one septic-fatal case, the successful use of penicillin for therapy supports its use as the treatment of choice for anthrax in endemic and enzootic regions. We also agree that penicillin is the antibiotic of choice for the treatment of naturally acquired human anthrax in Turkey. Although penicillin was found to be effective in the anthrax case series,[6,15,16,23] antibiotic susceptibility testing should be done in all isolates, especially when there is a biological warfare or terrorism possibility. In this situation, the strain may have been genetically altered to be resistant to penicilin.[29] In this retrospective study, antimicrobial susceptibility test had not been performed. This is considered as the limitation of our study. However, it was reported previously that all clinical *B. anthracis* strains from our region were found to be susceptible to penicillin.[34] No penicillin resistance for *B. anthracis* isolates from human cases have been reported in Turkey, up to date.[31] We think both the absence of penicillin resistant strains in Turkey and a high cure rate in our patients suggest that penicillin is still the first agent in the treatment of cutaneous anthrax. Corticosteroids were sometimes added to therapy if marked edema was present, particularly if airway compression occurred as a result of anthrax edema.[2,35] Systemic corticos-

teroids were added to the antibiotic treatment in our three patients with extensive edema. One septic case died despite antibiotic plus corticosteroid treatment. Untreated cutaneous anthrax is fatal in 20% of cases, but with the use of appropriate antibiotics, the mortality rate decreases to less than one percent.[2,3] In this study, the mortality rate was as low as 2.5%, comparable to other reports.[6,15,16,,23]

Cutaneous anthrax should be considered in any patient with a painless ulcer with vesicles, edema and a history of exposure to animals that are sick or have died from anthrax, or products derived from those animals. It has severe complications and fatal outcome when the diagnosis and treatment are delayed. Prevention of naturally-occurring anthrax in humans primarily depends on control of the disease in animals, especially livestock. Animal vaccination is the major means of preventing naturally occurring epizootics of anthrax, since widespread decontamination of infected soil is impractical. Annual vaccination of livestock in areas with enzootic anthrax is recommended.[5]

Since there was a history of slaughtering or exposure to infected animals in most of our cases, we suggest that preventive measures such as education of the high-risk population and vaccination of animals against anthrax may reduce anthrax prevalence in this region of Turkey. It seems that penicillin provides an effective and cheap treatment with rare adverse effects.

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