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A review of cutaneous anthrax and its outcome☆

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Abstract Anthrax is still an endemic disease in some countries in the world and has become a re-emerging disease in western countries with recent intentional outbreak. The aim of this study was to review our clinical experience with cutaneous anthrax cases. From the patient's files, transmission of the diseases, clinical findings and severity of infection, treatment and outcome of patients were recorded.

Twenty-two cases were diagnosed as cutaneous anthrax in the last 7 years. Of these cases, 10 cases were severe form of cutaneous anthrax, 10 cases were mild form and 2 cases were toxemic shock due to cutaneous anthrax. The incubation period was between 1 and 17 days. The main clinical characteristics of the cases with severe cutaneous anthrax were fever, hemorrhagic bullous lesions surrounded by an extensive erythema and edema, and leukocytosis. Two cases with toxemic shock had low systolic blood pressure, apathy and toxemic appearance, leukocytosis, hypoalbuminemia & hyponatremia. Penicillin G was given in 15 cases, amoxicillin in 4 and other antibiotics in 3 cases for 3—10 days. Skin lesion left deep tissue scar in 4 cases and were grafted.

Physicians working in endemic areas and also in western countries should be aware of all clinical forms of anthrax.

1. Introduction

Anthrax is usually a disease of herbivores and only incidentally infects humans. Humans almost always acquire anthrax directly or indirectly from infected animals. The main route of transmission is contact with or inhalation of *Bacillus anthracis* spores. Human cases may occur in an agricultural, an industrial environment or as a deliberately caused disease [1,2]. Although, this infection is a forgotten disease in western countries, it is still endemic in some parts of the world such as the Middle East,

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Central Asia and African countries [1—4]. In the September 11 attack in USA, 22 human anthrax (11 cutaneous and 11 inhalation) developed [5,6]. Just recently, two reports appeared from United Kingdom. Two inhalation anthrax cases (one in 2006 other in 2008) in bango drummer who used imported animal hides were reported and lastly an anthrax outbreak in drug users in Scotland was reported [7,8]. Anthrax has become a re-emerging disease in western countries and we can say anthrax is a global issue.

The disease occurs primarily in three forms: cutaneous, respiratory and gastrointestinal. Sepsis and meningitis can rarely develop after the lymphohematogenous spread of *B. anthracis* from a primary lesion. Cutaneous anthrax accounts for 95% of human cases globally. Data from pre-antibiotic and vaccine days indicated that 10—40% of untreated cutaneous anthrax cases might be expected to result in death. With the treatment, <1% cases are fatal. The clinical picture varies from mild to severe form. Cutaneous anthrax can be self-limiting, and lesions resolve without complications or scarring in 80—90% of cases with treatment. Extensive edema and toxemic shock can be seen as a rare and potentially life-threatening complication of cutaneous anthrax [1—3,9]. Human anthrax is decreasing by year in endemic areas. Older physicians are familiar with all clinical form of anthrax, but young physicians are not familiar with anthrax. For this reason, anthrax shows clinical diagnostic difficulties not only in western countries but also in endemic countries.

The aim of this study was to reevaluate our diagnosed cutaneous anthrax cases and there outcome.

2. Materials and methods

Medical records of Patient's diagnosed with cutaneous anthrax between 2002 and 2008 were reviewed and evaluated for infection source, lesion localization, severity of infection, complications, treatment and outcome at the Department of Infectious Diseases, Erciyes University Hospital, Kayseri, Turkey. The diagnosis was based on the history of an exposure to sick animals or animal products, clinical findings compatible with cutaneous anthrax, demonstration of gram-positive bacilli from a lesion, and/or isolation of *B. anthracis* from the lesion. The samples for Gram stain and culture were taken from the vesicles fluid or under the crust if developed. Skin biopsy was not performed.

A detailed history, including the occupation of the patient, exposure to a sick animal or animal products (such as slaughtering, butchering, chopping meat, touching an animal's raw skin), the time between a known exposure and the appearance of first lesion and antibiotic therapy received prior to admission was obtained from the patients upon hospital admission. Severity of the infection, lesion site, antibiotic treatment, duration of therapy, and outcome were recorded. In patients, peripheral blood count, blood biochemistry and chest X-ray were investigated routinely. Materials taken from the lesion and blood samples were cultured on sheep blood agar and in an automated blood culture system consecutively.

The patients were categorized into three groups according to clinical findings: mild cutaneous anthrax defined as the presence of a cutaneous lesion (<4 cm in diameter) surrounded a narrow erythema, but no systemic symptoms; severe cutaneous anthrax defined by the presence of a large cutaneous lesion with bullous reaction and extensive edema, and systemic symptoms including fever, tachycardia and tachypnea; toxemic shock defined by the presence of a cutaneous lesion, systemic symptoms including fever, tachycardia, tachypnea, acute mental changes and hypotension (systolic blood pressure <90 mmHg) and negative blood culture [1,3]. Bacteremia, superinfection and other organ involvement were also recorded.

3. Results

Twenty-two cases were evaluated. The median age was 44 (18—64). Seven out of 22 patients were female. Table 1 shows the characteristics and outcome of patients with cutaneous anthrax. Of these, 10 cases were diagnosed as mild form of cutaneous anthrax, 11 as severe cutaneous anthrax and 2 toxemic shock (one had severe cutaneous reaction and diagnosed as toxemic shock).

The clinical picture in mild cases was characterized by a typical cutaneous lesion less than 4 cm in diameter and surrounded by an erythema and low grade fever in the cases (Fig. 1). Leukocyte count was also below than $10^4/mm^3$ in these cases. The clinical presentation of a severe form of cutaneous anthrax in 11 cases was characterized with fever, hemorrhagic bullous lesions surrounded by an extensive erythema and edema and leukocytosis (leukocytes count was over 10^4/dl) (Figs. 2 and 3).

Clinical picture in 2 cases with toxemic shock was characterized with apathy and toxemic appearance, hypothermia (body temperature < 36 °C), extensive cutaneous inflammatory reaction with extensive edema, hypotension (sys-

Table 1 Demographic and clinical characteristics of patients with cutaneous anthrax.

Patient no	Age/gender	Duration of incubation (days)	Source of infection	Site of the lesion	Severity of infection	Gram stain[a]	Culture[a]	Previous antibiotic use (days)	Antibiotic therapy and route of administration	Duration of therapy (days)	Outcome
1	64 Female	7	Touching dead cattle	Right arm and left wrist	Severe cutaneous anthrax	Negative	Negative	Penicillin G + ciprofloxacin [1]	Penicillin G (intravenous)	10	Left deep scar, skin graft
2	30 Male	1	Carrying raw skin	Anterior neck	Toxemic shock,extensive edema	Positive	Negative	No	Penicillin G (intravenous)	7	*S. aureus* bacteremia, recovered
3	44 Male	3	Carrying dead animal carcass	Right arm	Severe cutaneous anthrax and extensive edema, toxemic shock	Negative	Positive	No	Penicillin G (intravenous)	5	Left deep scar, skin graft
4	33 Male	6	Handled ill cattle	Right and left arm	Severe cutaneous anthrax	Negative	Negative	Erythromycin 4 tablets	Penicillin G (intravenous)	5	Left deep tissue scar, skin graft
5	33 Male	6	Slaughtered and skinned dying sheep	Left hand and wrist	Severe cutaneous anthrax	Positive	Negative	Unknown	Clindamycin (intravenous)	5	Left deep tissue scar, skin graft
6	55 Female	6	Slaughtered dying sheep	Left hand finger	Mild cutaneous anthrax	Positive	Negative	One dose penicillin G	Amoxicillin (intravenous)	5	Recovered
7	18 Female	15	Slaughtered dying sheep	Left forearm	Mild cutaneous anthrax	Negative	Negative	Penicillin G [1]	Amoxicillin (oral)	3	Recovered
8	23 Male	12	Handled ill sheep	Left forearm	Mild cutaneous anthrax	Negative	Positive	No	Amoxicillin (oral)	5	Recovered

9	33 Male	7	Skinned dying sheep	Right hand wrist	Mild cutaneous anthrax	Negative	Negative	Cephalexin [2]	Procaine penicillin (intramus-cular)	5	Recovered
10	35 Female	17	Slaughtered and handled ill cattle	Right hand first finger	Mild cutaneous anthrax	Positive	Negative	No	Penicillin G (intra-venous)	5	Recovered
11	21 Female	3	Slaughtered and handled ill cattle	Right arm	Mild cutaneous anthrax	Negative	Negative	+[b]	Ciprofloxacin (intra-venous)	5	Recovered
12	27 Male	8	Handled and skinned dying sheep	Right arm	Severe cutaneous anthrax	Negative	Negative	+	Penicillin G (intra-venous)	5	Recovered
13	30 Female	4	Handled dying cattle	Left wrist	Severe cutaneous anthrax	Negative	Negative	No	Penicillin G (intra-venous)	10	Recovered
14	19 Male	8	Handled ill animals	Right hand	Severe cutaneous anthrax	Negative	Negative	Unknown	Penicillin G (intra-venous)	5	Recovered
15	52 Female	3	Handled and skinned dying sheep	Left hand and finger	Mild cutaneous anthrax.	Negative	Negative	+	Procain penicillin (intramus-cular)	7	Recovered
16	48 Male	5	Handled dying sheep	Left hand and finger	Severe cutaneous anthrax	Negative	Negative	Unknown	Penicillin G (intra-venous)	10	Recovered
17	30 Male	8	Handled dying sheep	Left hand wrist	Mild cutaneous anthrax	Negative	Negative	Unknown	Doxycycline (oral)	5	Recovered
18	39 Male	12	Handled ill cattle	Right hand	Mild cutaneous anthrax	Positive	Positive	No	Penicillin G (intra-venous)	10	Recovered
19	40 Male	?	Handled and skinned dying sheep	Right face	Severe cutaneous anthrax	Positive	Negative	+	Penicillin G (intra-venous)	10	Recovered

Table 1 (*Continued*)

Patient no	Age/gender	Duration of incubation (days)	Source of infection	Site of the lesion	Severity of infection	Gram stain[a]	Culture[a]	Previous antibiotic use (days)	Antibiotic therapy and route of administration	Duration of therapy (days)	Outcome
20	23 Male	?	Handled dying sheep	Right forearm	Severe cutaneous anthrax	Negative	Negative	Unknown	Penicillin G (intravenous)	5	Recovered
21	28 Male	2	Handled dying cattle	Right forearm	Severe cutaneous anthrax	Negative	Negative	Unknown	Penicillin G (intravenous)	10	Recovered
22	24 Male	5	Handled dying sheep	Right arm	Mild cutaneous anthrax	Negative	Negative	Unknown	Amoxicillin (oral)	5	Recovered

[a] The swabs for Gram stain and culture were taken from the vesicles fluid or under the crust if developed.
[b] These patients received oral antibiotics, however, the type of the antibiotic was unclear.

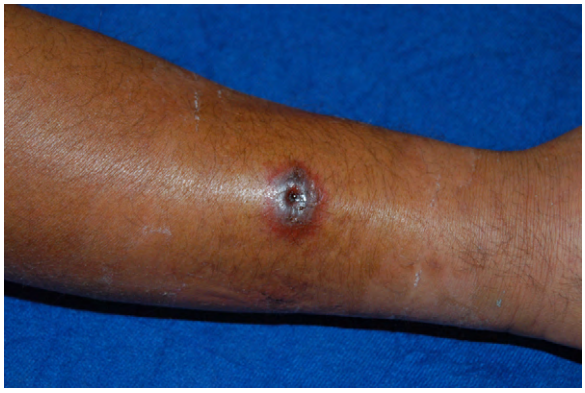

Fig. 1 Typical appearance of mild cutaneous anthrax characterized with central depressed, surrounded vesicle filled hemorrhagic fluid and erythema on the arm.

tolic blood pressure < 90 mmHg), leukocytosis with neutrophilia (WBC > $25 \times 10^3/mm^3$), hemaconcentration, hypoalbuminemia, hyponatremia and an increase in AST and ALT levels.

In the therapy, intravenous antibiotic and fluid infusion were given to 10 cases with severe cutaneous anthrax. Two cases diagnosed as toxemic shock were administered an antibiotic together with fluid infusion, albumin and vasoactive drugs. Intravenous penicillin was given to13 cases, intramuscularly procaine penicillin to 2 cases, oral amoxicillin to 4 cases and other antibiotics in 3 cases (ciprofloxacin in 1, doxycycline in 1 and clindamycine in 1). Antibiotic therapy was given to cases between 3 and 10 days (mean 5—7 days).

The lesions were healed with antibiotic therapy and the crust left no scarring in 18 cases but the lesions left deep tissue necrosis and scarring in 4 cases, and the wound was grafted in these cases (of these, 3 were severe cutaneous anthrax and 1 was severe cutaneous anthrax and toxemic shock). No deep organ involvement was seen in any of the cases as a complication. No superinfection in cutaneous lesion was seen but catheter related bacteremia due to Methicillin Sensitive *Staphylococcus aureus* (MSSA) was observed in 1 case with toxemic shock. No death was observed.

4. Discussion

Although anthrax is well controlled in the developed countries, anthrax remains of a global concern because *B. anthracis* spores can potentially be used as a biological weapon. On the other hand, some local anthrax outbreak has been recorded in western countries. For example, a case of naturally-acquired inhalation anthrax was reported

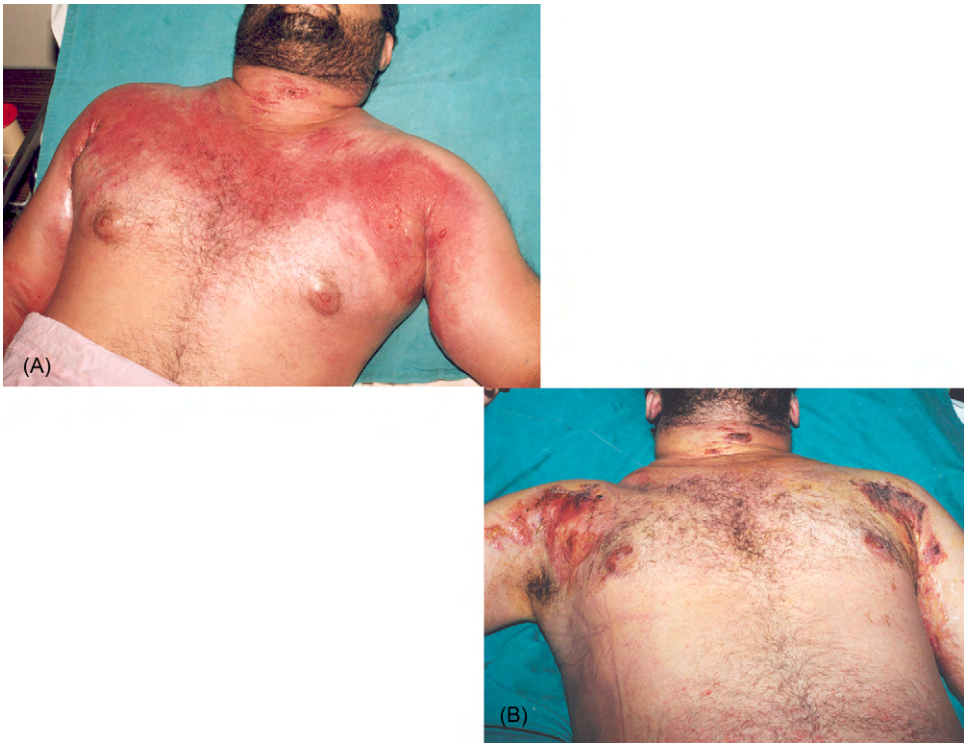

Fig. 2 Case 2. (A) He carried raw cattle skin. A pruritic lesion appeared on the anterior neck, after then, an extensive edema and erythema developed from the neck to anterior chest wall and both arms. The picture shows appearance of the lesion at the 8th day of disease. (B) 18th day of disease. Resolution of edema and occurrence of crust.

in London, 2008 and another case was recorded in Scotland in 2006. Both cases were bongo drummers/drum makers who used imported animal hides [7]. As of 14 January 2010, a total of 14 confirmed cases of anthrax infection in Scotland were reported and 7 of these died. All cases were heroin user. Possible source of infection is said that heroin is transported in animal skin [8]. In developed countries, there is also an infection risk after contact with a commercial product prepared from inadequately treated wool or leather. Products made from contaminated hair (e.g. shaving brush, wool coat), skins (e.g. drums, drumheads made from animal skin), and bone meal (e.g. fertilizer) may continue to be sources of infection for many years [1,3].

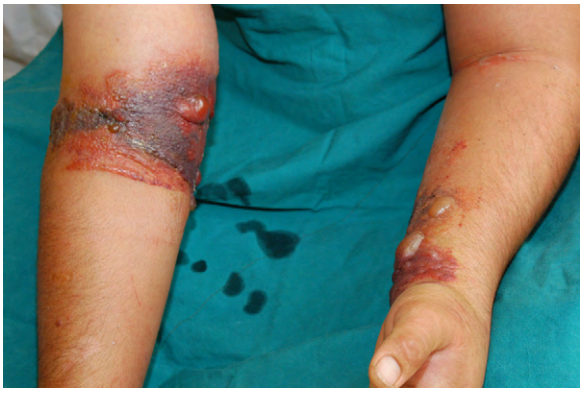

Fig. 3 Case 4. He handled cattle and 6 days later lesions had appeared on the right and left arms. An extensive edema and hemorrhagic bullae appeared on both arms. Typical appearance of severe cutaneous anthrax.

Anthrax is an endemic zoonosis in Turkey, particularly in the eastern part. The incidence of disease in Turkey has been decreasing with economic and social changes, strict animal vaccination programs and education of farmers [2,4]. According to the report of the Ministry of Health, 262 human cases were reported in 2007, 126 in 2008 and 132 in 2009 in Turkey. Most of the cases reported until today were cutaneous anthrax. Other clinical forms of anthrax, such as sepsis, meningitis, throat anthrax and intestinal anthrax were also reported before this study [2,10—14]. Anthrax occurs throughout the year in Turkey, but the majority of cases occur in the late summer and autumn which is the driest and hottest season [2,4]. Main source of transmission of the infection to human is generally thru contact with infected animal or contaminated animal products (such as skin, wool and meat) in Turkey, as presented cases in this paper.

The incubation period has been noted between 1 and 19 days, usually 2—7 days [1—3,9]. The incubation period ranged between 1 and 17 days for our case-series. The incubation period was 5 days (a range of 1—10 days) for the 11 cutaneous anthrax cases that were reported during 'anthrax letter' events in October—November 2001 in the United States of America [5].

A well-developed anthrax lesion can be easily recognized by physicians familiar with the disease. Unfortunately, few physicians are familiar with this clinical picture nowadays. The lesions are generally seen on an exposed area of the body, mostly on the face, neck, hands and wrist. Generally cutaneous lesions are single, but sometimes two or more lesions may be present [1—3,9—11,13]. In our cases, a single lesion was present in 18 patients and two lesions in 4 patients. Lesions were localized in hands and arms in 20 cases, on the neck in 1 case and on the face in 1 case.

Although the anthrax lesions were healed with antibiotic therapy, and the crust left no scarring in the mild cases, cutaneous lesions in severe cases left deep tissue necrosis and scarring in 4 cases in the 3rd week of disease. This eschar was removed surgically and grafted at 4—6 weeks of the disease.

Anthrax lesion begins to resolve after days 7—10 of the disease. Resolution takes several weeks and is not hastened by treatment. Time to resolution is dependent on the size, location and severity of the lesion. The initial crust separates several weeks after onset, with subsequent healing by granulation. Sometimes, the separation of the crust is delayed and the lesion may become secondarily infected. So, well-developed larger dried eschars were removed surgically in 4 cases. The most appropriate time for the skin grafting in these cases seems to be 4—6 weeks after the disease appears because inflammatory reaction and induration around the lesion is completely resolved during this period.

Airway obstruction by compression on the trachea from edematous swelling around neck, toxemic shock due to massive edema, sepsis, meningitis, temporal artery inflammation, deep tissue necrosis and secondary infection, and deep scar tissue were reported as complications in cases of cutaneous anthrax previously [1—3,11,13]. In our clinical experience, only 3 cases, including the 2 cases in this paper were diagnosed as toxemic shock due to massive edema. One case was reported before [14]. The main clinical and laboratory characteristics in two cases with toxemic shock are hypotension, low body temperature, tachycardia, tachypnea, mental changes, leukocytosis with neutrophilia, hyponatremia, increase in the level of AST, ALT and glucose, and a decrease in albumin level. The therapy may include volume replacement including fresh plasma and antibiotic administration. Corticosteroids and dopamine may be also given.

Penicillin G is still the drug of choice, and doxycycline or ciprofloxacin are now accepted as the best alternatives in the treatment of naturally-occurring anthrax. In the World Health Organization (WHO) Guidelines, intramuscular procaine penicillin, oral amoxicillin or penicillin V are recommended for the treatment of mild uncomplicated cases of cutaneous anthrax. Intravenous penicillin G is recommended in cutaneous anthrax with extensive edema [1].

The appropriate duration of treatment is debatable. *B. anthracis* cannot be isolated from cutaneous lesions 24—48 h after initiation of any antibiotic active against *B. anthracis*. Currently, WHO Guidelines is suggesting to continue antimicrobial therapy for 3—5 days (may be 3—7 days) in uncomplicated cutaneous anthrax although there is no controlled clinical study about the duration of treatment in cutaneous anthrax. Antibiotic treatment does not affect the progress of the lesion or other toxin-related systemic damage, and it does not alter the evolutionary stages. However, early treatment will limit the size of lesion. For this reason, early diagnosis of cutaneous anthrax and early initiation of therapy are very important. In our opinion, the duration of therapy may be adequate for 3—5 days in uncomplicated cutaneous anthrax.

As a summary, anthrax is an endemic diseases in Turkey as well as in some Middle East Countries. It is also threaten disease for western countries. Majority of cases are occurring in agricultural area. All clinical form can be seen but majority of cases are cutaneous anthrax. Clinical presentation of cutaneous anthrax may be mild or severe, and sometimes leads to severe complications such as sepsis, toxemic shock and other organ involvement. These clinical forms are a life-threatening complications of cutaneous anthrax. Early supportive treatment for these complications with appropriate antimicrobial therapy could be life-saving. Physicians, working not only in an endemic area for anthrax but also western countries, should be aware of all clinical forms of anthrax.*Funding*

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References

[1] Turnbull PCB.WHO Anthrax Working Group. Anthrax in humans and animals. 4th ed. Geneva: World Health Organization; 2008.

[2] Doganay M, Metan G. Human anthrax in Turkey from 1990 to 2007. Vector Borne Zoonotic Dis 2009;9(2):131—40.

[3] Doganay M. Anthrax. In: Cohen J, Opal SM, Powderly WG, editors. Infectious diseases. 3rd ed. China: Mosby-Elsevier; 2010. p. 1257—61.

[4] Ozkurt Z, Parlak M, Tastan R, Dinler U, Saglam YS, Ozyurek SF. Anthrax in eastern Turkey, 1992—2004. Emerg Infect Dis 2005;11:1939—41.

[5] Jernigan JA, Stephens DS, Ashford DA, et al. Bioterrorism-related inhalation anthrax: the first 10 cases reported in the United States. Emerg Infect Dis 2001;7:933—44.

[6] Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, et al. Working group on civilian biodefense. Anthrax as a biological weapon. JAMA 2002;287:2236—52.

[7] Anaraki S, Addiman S, Nixon G, et al. A case of naturally acquired inhalation anthrax in London. In: Bacillus-ACT 2009: the international *Bacillus anthracis*, *B. cereus*, and *B. thuringiensis* conference, an ASM conference. 2009. Abstract number: 16 D.

[8] Ramsay CN, Stirling A, Smith J, et al. An outbreak of infection with *Bacillus anthracis* in injecting drug users in Scotland. Eurosurveillance 2010;15(2).

[9] Dixon TC, Messelson M, Guillemin J, Hanna PC. Anthrax. New Eng J Med 1999;11:815—26.

[10] Demirdag K, Ozden M, Saral Y, Kalkan A, Kilic SS, Ozdarendeli A. Cutaneous anthrax in adults: a review of 25 cases in the eastern Anatolian region of Turkey. Infection 2003;31:327—30.

[11] Kaya A, Tasyaran MA, Erol S, Ozkurt Z. Anthrax in adults and children: a review of 132 cases in Turkey. Eur J Clin Microbiol Infect Dis 2002;21:258—61.

[12] Tasyaran MA, Deniz O, Ertek M, Cetin K. Anthrax meningitis: case report and review. Scan J Infect Dis 2002;34:66—7.

[13] Smego RA, Gebrian B, Desmangels G. Cutaneous manifestations of anthrax in rural Haiti. Clin Infect Dis 1998;26:97—102.

[14] Doganay M, Bakır M, Dokmetas I. A case of cutaneous anthrax with toxaemic shock. Br J Dermatol 1987;117:659—62.