You are building relationships with a tribe that primarily inhabits the border region between Iraq and Syria when you are asked to examine a skin lesion on a young adult male in the village. The lesion (Photo 1) on his forearm is four days old as described by the translators. On physical exam you note the patient to be afebrile, has the cutaneous lesion shown in Photo 1, and has shotty epitrochlear nodes and axillary lymphadenopathy. You treat this as a standard carbuncle with some oral antibiotics and instruct him to follow-up if the lesion persists or acutely changes. The translator runs you down a few days later and brings the patient back to the team area. Now the lesion has progressed to a painless blackened presentation as illustrated in Photo 2. He is now febrile and on physical exam you find an additional lesion on his right neck as illustrated in Photo 3.

Using the primary lesion definitions outlined in your SOF medical handbook, how would you describe the morphology of these lesions?

What is the differential diagnosis of these lesions?
**ANSWERS**

Morphology lesion Photo 1—**Erythematous Papule**: A solid lesion, usually dome-shaped, <1 cm in diameter and elevated above the skin.\(^1\)

Morphology lesions Photos 2 and 3—**Ulcer**: Loss of epidermis and at least part of dermis that results in scarring, with black eschar.\(^1\)

**DIFFERENTIAL DIAGNOSIS**

Photo 1: Has a very broad differential that includes actinic keratosis, angiofibroma, basal cell carcinoma, dermatofibroma, an early bacterial or fungal infection, hemangioma, amelanotic melanoma, molluscum contagiosum, neurofibroma, nevus, pyogenic granuloma, or squamous cell carcinoma.\(^2\)

Photos 2 and 3: Cutaneous anthrax, brown recluse spider bite, eczema, ulceroglandular tularemia, accidental vaccinia, necrotic herpes simplex infection, orf, glanders.\(^3\)

**CUTANEOUS ANTHRAX**

**EPIDEMIOLOGY**

*Bacillus anthracis* has a nearly worldwide distribution, existing in the soil as an extremely resistant spore. More than 95% of naturally occurring anthrax is the cutaneous form. Under natural non-bioterroristic conditions, humans usually acquire anthrax infections from contact with infected animals or contaminated animal products, such as hides, wool, and hair.

Between 20,000 and 100,000 cases of anthrax have been estimated to occur worldwide annually. However, in the United States early in the 20th century, the annual incidence was 127 and declined to less than one. This low annual incidence rate has been consistent for the last 20 years, until the recent terrorist act utilizing anthrax in 2001.\(^4\)

Epizootic anthrax will continue to occur in highly endemic areas, such as Iran, Iraq, Turkey, Pakistan, and sub-Saharan Africa, where the use of animal anthrax vaccine is not comprehensive. In 2001, there were 22 confirmed or suspected cases of anthrax related to the terrorist act of mailing anthrax spores in the Eastern United States. Eleven of these cases were inhalational and the other 11 cutaneous. Four of the people died of inhalational anthrax.\(^5\)

**ETIOLOGY/PATHOGENESIS**

Cutaneous anthrax is a bacterial infection caused by the endospores of *Bacillus anthracis*. Anthrax can infect the individual’s lungs through inhalation, the gastrointestinal tract through ingestion, and/or the skin through cutaneous abrasions. *B. anthracis* is a non-motile, gram-positive, aerobic rod, 1.2 to 10 micrometers in width (Photo 4). Spores can remain dormant in soil for decades, in virtually any weather condition.\(^3\)

Anthrax spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as the blood and/or tissue in either animals or humans. The replicating bacteria produce at least three pathogenic proteins: protective antigen (PA), lethal factor (LF), and edema factor (EF). These proteins combine to form two toxins known as lethal toxin and edema toxin.\(^6\)

**CLINICAL**

Over 90% of cutaneous anthrax lesions occur in exposed areas such as the face, neck, arms, and hands. The reported incubation period for cutaneous anthrax is from one to twelve days. Skin infections begin as a small papule that may be pruritic, progresses to a vesicle in one to two days, which then erodes, leaving a necrotic ulcer with a characteristic black central eschar. Secondary vesicles around the primary lesion may develop. The lesion is usually painless; however, other symptoms may include swelling of adjacent lymph nodes, fever, malaise, and headache. The diagnosis of cutaneous anthrax is suggested by the presence of the eschar, the presence of edema out of proportion to the size of the lesion, and the lack of pain during the initial phases of infection.\(^6\)
The diagnosis of cutaneous anthrax should be suspected by the characteristic painless, shallow ulcer with black crust (Photos 2 and 3). Gram stain of vesicular fluid will reveal typical gram-positive bacteria (Photo 4). Diagnosis can be confirmed by tissue culture and polymerase chain reaction (PCR) studies that are available through Landstuhl Regional Medical Center (LRMC) for the indicated areas of operation.6 It should be noted that one is not considered at risk for contracting pulmonary anthrax when evaluating a patient with cutaneous anthrax since the disease is acquired through contact with anthrax spores, not active bacteria.7

Specimens should be collected from any patient being evaluated for cutaneous Bacillus anthracis infection. The CDC recommends that the following procedure be used for cutaneous anthrax testing. Initially, regardless of the stage of the lesion, collect two separate swabs: one swab for Gram stain and culture and one swab for PCR. If lesions are in the vesicular stage, aseptically collect vesicular fluid on sterile dry swabs from previously unopened vesicles. In addition, it should be noted that anthrax bacilli are most likely to be observed on Gram stain in the vesicular stage. When lesions are in the eschar stage, collect eschar material by carefully lifting the eschar’s outer edge. Insert a sterile dry swab, then slowly rotate for two to three seconds, beneath the edge of the eschar without removing it. If the lesion is in the ulcer stage and no vesicle or eschar is present, swab the base of the ulcer using a sterile saline, pre-moistened swab. Specimens intended for culture, or both culture and PCR, should be shipped using cold packs and stored at 2 to 8°C. Specimens intended only for PCR testing may be shipped on dry ice and stored at -70°C.8

A skin biopsy should be obtained on every patient with a lesion being evaluated for cutaneous anthrax. If the patient is on antimicrobial therapy at the time of presentation, obtain one full thickness 4mm punch biopsy sample from a papular or vesicular lesion and include adjacent normal skin. Place the specimen in the standard 10% buffered formalin for histopathology. If the patient has not received antibiotics or if antibiotic therapy has been initiated in the proceeding 24 hours, obtain a second full thickness punch biopsy specimen for culture, Gram stain, PCR and frozen tissue for immunohistochemical studies. Do not attempt to split one 4mm sample for all of the studies. Biopsies should be taken from both vesicular and escharred lesions if present. Fresh samples (not formalin fixed) should be stored and shipped frozen to LRMC in this area of operation (or your closest major medical center in other settings) at -70°C and formalin fixed samples should be shipped at room temperature. More specific guidelines on collection of these specimens are provided in Shieh et al., American Journal of Pathology, Nov 2003, Vol 163, No. 5, Page 1908, Column 2.8

Acute serum specimens should ALWAYS be collected within the first seven days of symptom onset or as soon as possible after known exposure. Even if the diagnosis of anthrax is confirmed by isolation of B. anthracis from clinical specimens, collect a convalescent serum sample, 14 to 35 days after symptom onset. Both acute and convalescent serum specimens should be obtained with a minimum of 8ml blood, yielding ~ 4ml of sera.

If the patient has evidence of systemic symptoms, specimens for blood culture should be obtained. Collect two sets of cultures and a 10ml blood sample in EDTA (purple top tubes) for PCR testing.8

**Therapy**

For cutaneous anthrax, ciprofloxacin or doxycycline is the recommended first line therapy. Intravenous therapy is recommended for cutaneous anthrax with signs of systemic involvement, for extensive edema, or for lesions on the head or neck (Tables 1 and 2). Cutaneous anthrax is typically treated for seven to ten days. However, in the setting of a bioterrorism attack or deployment, the risk for simultaneous aerosol exposure may be high. As a result, persons with cutaneous anthrax associated with bioterrorism or deployment to OIF/OEF should be treated for 60 days.9

Treatment of cutaneous anthrax with antibiotics does not stop nor delay the normal progression of the lesion through the eschar phase. Antibiotics are given in hopes of eliminating the chance of this localized cutaneous infection transitioning to a systemic infection and causing significant mortality and increased morbidity. The case-fatality rate of cutaneous anthrax is five to twenty percent without antibiotic treatment, and less than one percent with antibiotic treatment.4
Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Initial therapy (oral)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults*</td>
<td>Ciprofloxacin 500 mg BID or Doxycycline 100 mg BID</td>
<td>60 days*</td>
</tr>
<tr>
<td>Children*</td>
<td>Ciprofloxacin 10-15 mg/kg every 12 hrs (not to exceed 1 g/day) or Doxycycline 300 mg/day</td>
<td>60 days*</td>
</tr>
<tr>
<td></td>
<td>&gt;8 yrs and &lt;45 kg: 100 mg every 12 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;8 yrs and ≤45 kg: 22 mg/kg every 12 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤8 yrs: 22 mg/kg every 12 hrs</td>
<td></td>
</tr>
<tr>
<td>Pregnant women***</td>
<td>Ciprofloxacin 500 mg BID or Doxycycline 100 mg BID</td>
<td>60 days*</td>
</tr>
<tr>
<td>Immunocompromised persons*</td>
<td>Same for nonimmunocompromised persons and children</td>
<td>60 days*</td>
</tr>
</tbody>
</table>

* Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended. Table 1.
* Ciprofloxacin or doxycycline should be considered first-line therapy. Amoxicillin 500 mg po TID for adults or 80 mg/kg/day divided every 8 hours for children is an option for completion of therapy after clinical improvement. Oral amoxicillin dose is based on the need to achieve appropriate minimum inhibitory concentration levels.
* Previous guidelines have suggested treating cutaneous anthrax for 7-10 days, but 60 days is recommended in the setting of this attack, given the likelihood of exposure to aerosolized B. anthracis (B).
* The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (e.g., Rocky Mountain spotted fever).

** Although tetracyclines or ciprofloxacin are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose-related; therefore, doxycycline

Table 2

<table>
<thead>
<tr>
<th>Category</th>
<th>Initial therapy (oral)</th>
<th>IV treatment initially**</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Ciprofloxacin 500 mg every 12 hrs*</td>
<td>Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg po BID or Doxycycline 100 mg po BID</td>
<td>60 days IV and po combined**</td>
</tr>
<tr>
<td></td>
<td>Doxycycline 100 mg every 12 hrs*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One or two additional antimicrobial*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Ciprofloxacin 10-15 mg/kg every 12 hrs***</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline 300 mg/day</td>
<td></td>
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<td>≤8 yrs: 22 mg/kg every 12 hrs</td>
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</tr>
<tr>
<td></td>
<td>One or two additional antimicrobial*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant women***</td>
<td>Same as nonpregnant adults: high risk from the infection outweighs the risk posed by the antimicrobial agent</td>
<td>IV treatment initially**: Switch to oral antimicrobial therapy when clinically appropriate. Oral therapy regimen same for nonpregnant adults</td>
<td>60 days IV and po combined**</td>
</tr>
<tr>
<td>Immunocompromised persons*</td>
<td>Same for immunocompromised persons and children</td>
<td>IV treatment initially**: Switch to oral antimicrobial therapy when clinically appropriate. Oral therapy regimen same for nonpregnant adults</td>
<td>60 days IV and po combined**</td>
</tr>
</tbody>
</table>

* For gastrointestinal and ophthalmic anthrax, see regimen recommended for inhalational anthrax.
* Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.
* Doxycycline may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with Bacillus anthracis meningitis.
* Other agents with in vitro activity include rifampin, vancomycin, penicillin, amikacin, clindamycin, and chloramphenicol. Because of concerns of gastrointestinal and cutaneous side effects, tetracyclines, penicillin, and amikacin should not be used alone. Consultation with an infectious disease specialist is advised.
** Initial therapy may be altered based on clinical course of the patient, (one or two antimicrobial agents) e.g., ciprofloxacin or doxycycline may be adequate as the patient improves.
* If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.
* Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.
* If inhalational ciprofloxacin is not available, and ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are obtained 1-2 hours after oral dosing but may not be achievable if vomiting or diarrhea are present.
* For children, ciprofloxacin dosing should not exceed 2.5 g/day.
* This American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections. c.g., Rocky Mountain spotted fever.
* Although tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose-related; therefore, doxycycline might be used for a shorter time (7-14 days) before 6 months of gestation.
If you are DEPLOYED and have concerns about a puzzling skin condition, you can email your clinical photos and a concise morphologic description of the lesion to our Operational Teledermatology site at derm.consult@us.army.mil or directly to Daniel.Schissel@us.army.mil. The lesion you describe just may make its way to the next edition of Picture This...

Thanks for all you do.

LTC Michael Rossman is a 1994 graduate of Texas A&M College of Medicine. He completed his internship and residency with the internal medicine department at Madigan Army Medical Center, Fort Lewis, WA. LTC Rossman served as the battalion surgeon for 1/16th IN for SFOR 6 and was a flight surgeon in Heidelberg, Germany. Later he was the brigade surgeon for 1st BDE (Stryker) 25th ID in Mosul, Iraq for OIF III and is currently the chief, Department of Primary Care at Heidelberg MEDDAC as well as the European Regional Medical Command (ERMC) Flight surgeon consultant.

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8. CDC, Emergency Preparedness and response website – laboratory information: Cutaneous Anthrax: Recommended Specimens for Microbiology and Pathology for Diagnosis.