

Brief Report

GLANDERS IN A MILITARY RESEARCH
MICROBIOLOGIST

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INFECTION with *Burkholderia mallei* (formerly *Pseudomonas mallei*) can cause a subcutaneous infection known as farcy or can disseminate to cause the condition known as glanders. In humans, acute infection with *B. mallei* is characterized by necrosis of the tracheobronchial tree, pustular skin lesions, and either a febrile pneumonia, if the organism was inhaled, or signs of sepsis and multiple abscesses, if the skin was the portal of entry.¹ At the turn of the 20th century, glanders was an important cause of death among horses, and there were secondary, often fatal, infections in humans.² Because of the lethal and contagious nature of the disease, *B. mallei* was considered an ideal agent for biologic warfare and was used for this purpose by Germany in World War I.³

Aggressive control measures essentially eliminated glanders from the West. However, with the resurgent concern about biologic warfare, *B. mallei* is now being studied in laboratories worldwide. We describe here the first reported case of human glanders in the United States in more than 50 years and discuss some of the important events in the history of the disease and its initial eradication.

CASE REPORT

In March 2000, tender, left axillary adenopathy and fever (temperature, 38.6°C) developed in a 33-year-old microbiologist at the U.S. Army Medical Research Institute for Infectious Diseases who had type 1 diabetes mellitus. The patient had worked for two years investigating the basic microbiology of *B. mallei* and did not routinely wear latex gloves. The adenopathy and fever persisted despite treatment for 10 days with a first-generation cephalosporin. An evaluation after this treatment, which included chest radiography as well as cultures of blood and urine, was unrevealing. During the next few weeks, the patient had increasing fatigue, night sweats, malaise, rigors, and weight loss.

In early April, his symptoms and adenopathy resolved during a

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10-day course of clarithromycin, but he relapsed 4 days after the medication was stopped. On May 2, he was admitted to his local hospital with diabetic ketoacidosis. A computed tomographic (CT) scan showed multiple hepatic and splenic abscesses (Fig. 1A). On May 4, respiratory distress requiring mechanical ventilation developed, and the patient was transferred to Johns Hopkins Hospital in Baltimore.

Physical examination revealed a temperature of 40.3°C and a heart rate of 122 beats per minute. The patient had a grade 2/6 systolic murmur, coarse breath sounds, and moderate epigastric tenderness. Laboratory studies showed a white-cell count of 8300 per cubic millimeter, with 83 percent neutrophils, 9 percent monocytes, and 8 percent lymphocytes. The hematocrit was 25.6 percent. The concentrations of aspartate aminotransferase and alanine aminotransferase were 53 U per liter and 56 U per liter, respectively, and the alkaline phosphatase was 197 IU per liter. Cultures of the patient's blood and a sample from a fine-needle aspiration biopsy of a liver abscess grew a small, bipolar, weakly staining, gram-negative rod that was identified by an automated bacterial-identification system as *Pseudomonas fluorescens* or *P. putida*. However, gas-liquid chromatography of the cellular fatty acids (Microbial ID, Newark, Del.) placed the organism in the genus *Burkholderia*. Subsequent phenotypic testing and 16S ribosomal RNA gene-sequence analysis identified the organism as *B. mallei* (Fig. 2). Initial susceptibility testing showed the isolate to be sensitive to imipenem, ceftazidime, and tetracycline.

The patient was treated with imipenem and doxycycline, and there was rapid improvement. After two weeks, the imipenem was replaced by azithromycin, and the patient completed a six-month course of treatment with azithromycin and doxycycline. Although the organism was found retrospectively to be relatively resistant to azithromycin, a CT scan obtained after six months of treatment showed substantial improvement of the liver and spleen abscesses (Fig. 1B), and one year later the patient remained in good health.

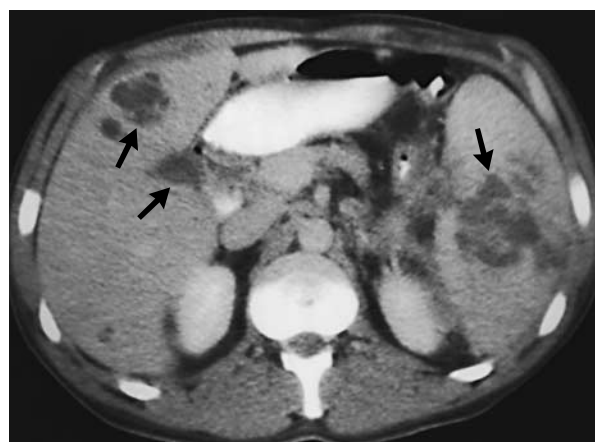
DISCUSSION

This is the first reported human case of glanders in the English-language medical literature since 1949,⁴ and it occurred in the context of research on agents of biologic warfare.

Glanders may have been the first biologic weapon of the 20th century. During World War I, Germany had a program of biologic sabotage against several countries, including the United States, whereby cultures of *B. mallei* and anthrax were distributed to undercover agents who attempted to infect livestock that were to be shipped to Allied countries.³ The intention was both the destruction of livestock and the transmission of the highly contagious, lethal agent from livestock to humans. It is currently suspected that attempts are being made to develop an aerosolized form of antibiotic-resistant *B. mallei* that could become a biologic weapon as potent as anthrax.

Glanders, an important human and veterinary disease, was eliminated without a vaccine or effective treatment. It appears to have been abolished by the veterinary use of a skin test to detect exposure to *B. mallei* combined with draconian agricultural measures to control infection.⁵

At the turn of the 20th century, Canada, Britain, and the United States all implemented glanders-control programs. By that time, the symptoms of equine glanders, which include fever and inflammation of the nasal mucosa with ultimate necrosis and obstruction



A



B

Figure 1. Pretreatment (Panel A) and Post-Treatment (Panel B) Abdominal Computed Tomographic Scans from a Patient with Glanders.

Panel A shows multiple hepatic and splenic abscesses (arrows), and Panel B shows nearly complete resolution of the abscesses.

of the oropharynx, had been well described.⁶ Laws were passed that required notification of the health department and the immediate slaughter of affected animals, with proper disposal of the carcasses. In addition, all horses on the premises where the infected horses were found had to be tested with the mallein skin test for exposure to *B. mallei*; any horses with a reaction also had to be slaughtered. Horses with no reaction were quarantined and then retested two to three weeks later. Furthermore, the equine contacts of the horses were traced to track down other horses that might have been exposed and then moved to other facilities.

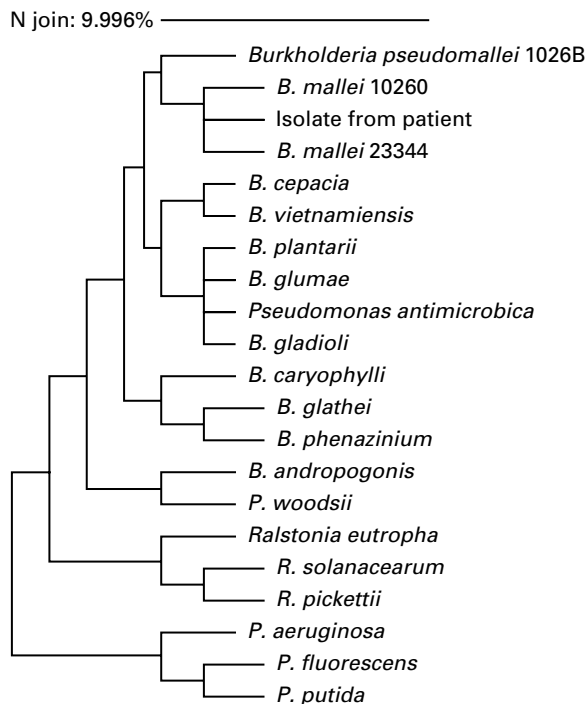


Figure 2. Phylogenetic Tree Derived from 1.5-kb Nucleotide Sequences of 16S Ribosomal RNA from the Infecting Organism and Other Related Isolates from the Johns Hopkins Microbiology Laboratory and GenBank.

The tree was constructed on the basis of neighbor-joining (N join) analysis. *Pseudomonas aeruginosa* was used as an outgroup. Numbers beside strains are the American Type Culture Collection reference numbers of the strains we sequenced. The genetic distance between two species is obtained by adding the lengths of the connecting horizontal lines. The length of the bar at the top denotes a sequence divergence of 9.996 percent.

The case we describe illustrates the major clinical features of glanders, which can usually be traced to direct contact with *B. mallei*, as in workers exposed to animals with glanders⁷ and in personnel who were exposed in laboratories during World War II.⁸ Although the patient discussed here could not recall a clear break in his skin or an accident in the laboratory, most reported occupational infections occur without recognized instances of exposure.⁹ As Robins commented in 1906, "It is perhaps not advisable to be too dogmatic as to the invariable necessity of an abrasion being present in every case of human glanders . . . [as] in several such cases of our series it is distinctly stated that there was no abrasion."⁷ As in our patient, *B. mallei* often enters the body through the hand or arm. After an incubation period lasting between a few days and several weeks, local suppuration and regional lymphadenopathy occur. Constitutional symptoms often accompany the infection, with fever, rigors, and malaise predominating. If the infection is left un-

treated, abscesses in the lymph nodes will generally form, then break down and drain.

Dissemination of the infection occurs one to four weeks after infection of the lymph nodes. Abscesses can be widespread, and *B. mallei* can infect almost any tissue.⁷ Abscesses in the liver and the spleen, as were seen in our patient, appear to be relatively common, as does pulmonary involvement, including consolidation, abscesses, and pleural nodules. The acute onset and rapid resolution of the respiratory failure in our patient were more consistent with the respiratory distress syndrome associated with gram-negative bacteremia than with that associated with pulmonary glanders. Subcutaneous and intramuscular abscesses sometimes develop as well.⁷

There are few data regarding the antibiotic treatment of glanders, since the disease had largely disappeared by the time antibiotics became available. In vitro, ceftazidime, gentamicin, imipenem, doxycycline, and ciprofloxacin all have reliable activity against *B. mallei*,¹⁰ and our patient's infection responded well to a combination of imipenem and doxycycline. Experimentally induced glanders also responds to a combination of sulfazine and trimethoprim.¹¹ However, treatment of the disease in the setting of bioterrorism may be more difficult if the organism is drug-resistant.

This case demonstrates the difficulties that microbiology laboratories may have in recognizing potential agents of biologic warfare. These microbes are rarely encountered and may be misidentified by conventional, phenotypic identification systems. Techniques such as cellular analysis of fatty acid and 16S ribosomal RNA gene sequencing can be used to identify the organisms correctly, but these tests are not widely available.

Finally, this case may serve as a harbinger of the re-

surge of nearly forgotten diseases such as glanders, plague, smallpox, and anthrax. Research on these diseases is now being conducted in more laboratories, which increases the risk of occupational exposure. There is also the looming threat that some group will eventually mount a successful campaign of bioterrorism. Resources must be allocated both to prevent and to prepare for these frightening possibilities.

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