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The Anthrax Disease in Iran From 2000 to 2016: The Predominance of Cutaneous and Gastrointestinal Form

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Abstract

Context: Anthrax is a zoonotic and occupational disease caused by bacterium *Bacillus anthracis*. The agent produces spores which persist in the environment for years. This review assessed previous reports on anthrax disease in Iran from 2000 to 2016.

Evidence acquisition: The reports of anthrax from 2000 to 2016 were reviewed. The keywords "*Bacillus anthracis*", "Anthrax", "clinical signs", "Iran" and "zoonosis" were investigated in the searching databases such as "Google Scholar", "Google", "PubMed" and other sites. The reports of soil isolation and spores from environments were excluded. However, the clinical outcome of the cases, history of animal exposure, wool contaminations and meat in slaughterhouses were included. Results of Persian reports were also included in this review. Data were analyzed using Excel and GraphPad Prism version 6.1. The standardized mean difference (SMD) was used for data analysis.. Overall, 768 cases of anthrax were found in human, sheep, goats and cattle. Six hundred of the human cases aged between 2.5 and 71 years old were included. Four-hundred ten (68.33%) patients were male (mean age=28.1 ± 1.5) and 190 (31.66%) patients were female (mean age = 17±1.5). Clinical manifestations in patients were mostly in 2 cutaneous (56.6%) and gastrointestinal (42.83%) forms. Sporadic anthrax outbreaks occurred in the country in 2007, 2008 and 2011. No molecular typing has been performed for *B. anthracis* strains countrywide. The virulence factors encoded by the genes located on plasmids pXO1 and pXO2 were detected in various areas with high prevalence.

Conclusion: Cutaneous and gastrointestinal anthrax are 2 main manifestations of the disease in Iran. Male patients were significantly more infected. Although rare, anthrax continues to be a dreadful consequence of herds or soil exposure and consumption of undercooked meat of infected animals. Education plans and proper animal vaccination plans with the consideration of virulence factors are helpful for the prevention of the disease.

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Context

Anthrax is a zoonotic disease caused by *Bacillus anthracis* that killed half of the sheep in Europe in early 18th century and approximately 1 million in Iran in 1945.[1] Its ecology is associated with many factors such as the effects of flood-drought cycles, soil qualities,[2,3] soil flora and is transported by insects.[4-6] *B. antharacis* is a gram-positive non-motile spore-forming agent producing 3 toxins (lethal toxin, protective antigen and edema factor) and capsule encoded by 2 plasmids called pXO1 and pXO2 respectively.[7,8] *B. anthracis* is considered among the most important biological warfare agents because of highly pathogenic nature and spore-forming capability of strains that are extremely resistant to natural conditions.[9] In 2001, bioterrorist activities in the United States Postal Service infected 22 people.[10] The disease occurs when *B. anthracis* endospores enter the body and initiate the infection either through breaks in the skin, ingestion, or inhalation.[11] Two reasons for highly lethal nature (50%-90%) of inhalation form have been suggested as follows: toxemia model and overwhelming bacteremia leading to severe sepsis.[12,13] Two cases of anthrax were reported in heroin users in Scotland, which were subsequently spread into England and Germany.[14] An inhalation form with an unknown source was diagnosed in a patient in the United States.[15] The incubation period may be as short as 12 to 15 hours.[9] The inhalational form is the most fatal form of anthrax infection, followed by gastrointestinal and cutaneous forms, however, all of them might have a fatal outcome, especially when antibiotic therapy is delayed. The cutaneous form may be misdiagnosed as orf and tularemia, and thus the diagnosis needs to be performed as soon as the signs are observed. There are some reports of gastrointestinal, cutaneous and rare cases of eyelid

and meningitis anthrax from different cities of Iran.[16,17] GI anthrax has been reported in Shiraz, Mazandaran, Rasht, Mashhad, Kermanshah and several other areas.[18] All of these cases were caused via consumption of sheep and goat meat. GI form is endemic in southern India and a case of GI with sepsis and disseminated intravascular coagulation was reported in a patient that had eaten raw meat under the influence of alcohol.[19] Since February 29, 2016, no case of inhalational anthrax has been determined in Iran. Areas with higher endemicity of anthrax include sub-Saharan Africa, Southeast Asia, and parts of the former Soviet Union.[20] In Bangladesh, 273 human cases of cutaneous anthrax were reported among which 91% of persons had a history of contact with animals or consuming meat in 2009-2010.[21] The aim of this review was the assessment of anthrax disease in Iran from 2000 to 2016.

Evidence Acquisition

In this review, the medical and veterinary records of anthrax from 2000 to 2016 were included. The words of "*Bacillus anthracis*", "Anthrax", "prevalence", "Iran" and "zoonosis" were searched in the searching engines such as "Google Scholar", "Google", "PubMed", "Science Direct" and other sites. The reports of soil isolation and spores from environments were excluded. However, the clinical outcome of the cases, history of animal exposure, wool contamination and meat in slaughterhouses were included. Results of Persian reports were also included in this review. Data were analyzed using Excel, SPSS and GraphPad Prism 6 software. The standardized mean difference (SMD) was used for data analysis. All the data were saved in Excel and arranged, and then transmitted to the GraphPad Prism and later were analyzed.

Anthrax Cases and Clinical Manifestations

Overall, 768 cases of anthrax have been isolated from human, sheep, goats and cattle between 2000 and 2016 all over Iran. Six hundred human cases between the ages of 2.5 and 71 years were included. Four hundred ten (68.33%) patients were male (mean age = 28.1±1.5) and 190 (31.66%) were female (mean age = 17±1.5). Unfortunately, 7 patients aged 15, 34, 26, 21, 53, 17 and 24 years have died despite penicillin G treatment, all with GI infection. Clinical manifestations in patients were mostly in 2 cutaneous (56.6%) and GI (42.83%) forms because of the exposure to farm animals or soil and eating undercooked meat and liver of the infected sheep or goats (Figure 1). Most of the cutaneous infections were on hands and faces of patients. Moreover, among patients with GI infection, vomiting, abdominal pain, bloody stool and hemorrhage of upper and lower gastrointestinal tract were mostly observed. In the year 2002, 269 human cases of multi-species anthrax (according to the OIE) were reported. Moreover, 250 in 2003, 155 (with 1 death) in 2005 and 165 cases (with 1 death) were diagnosed in 2007. In 2008, 150 cases were detected.[22] These results showed a constant threat to the people in the country; especially considering the soil as a natural contamination. While 8 outbreaks of bovine were reported in 2007, 33 cases were reported in 2008. Furthermore, 5, 1, 28, 1, 6, 3 and 3 isolates were reported in 2009,[23] 2010, 2011, 2012, 2013, 2014 and 2015, respectively, however, no clinical report was found in 2016. GI, cutaneous, meningitis and eye infection were reported in these studies. In addition, an epidemic of cutaneous form (28 cases) occurred in Esfarayen, a city in Northeast Iran, in 2011.[18,19,24-28] Moreover, studies of human, sheep, cattle, goat and soil samples in several areas of Iran showed that all *B. anthracis* isolates were pXO1 and pXO2 positive, emphasizing the countrywide presence of highly pathogenic strains.[17] The mean of encapsulated pathogens from several other studies was 50.5%.

Countrywide Trends in the Anthrax Disease From Past Until Recent Years

Various reports worldwide emphasize the zoonotic nature of anthrax disease mainly transmitted through animal exposure and consumption of raw or undercooked meat.[29,30] The disease is still present worldwide naturally and is problematic in many countries and regions.[31] From 600 reports in Iran between 2000 and 2016, nearly all infections were occurred because of the contact with herd and meat consumption, showing the importance of farm animals in the spread of this disease. Animal-mediated transmission and even outbreaks of the disease have been reported in other areas of the world mostly because of the infection of herbivores.[32-34] The contamination can take place everywhere, and this necessitates the education and awareness in this regard.[35] The infection happened in all ages between 2.5 and 71 years old but the higher infection occurred among men in the age range of 20 to 30 years old. In this study, 410 (68.33%) patients were male showing a significant ($P = 0.02$) higher rate compared to 190 (31.66%) female patients. This result

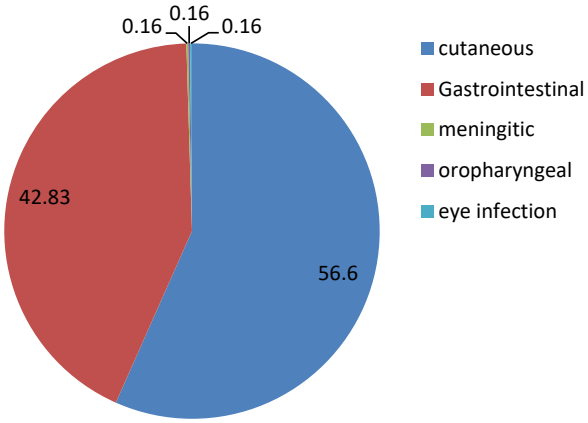

Figure 1. Clinical manifestations of *Bacillus anthracis* Isolates in Humans

highlights the occupational aspect of the disease in the country and higher exposure of male individuals to the livestock or any meat products and soil. Unfortunately, 7 patients aged 15, 34, 26, 21, 53, 17 and 24 years had died despite penicillin G treatment, all with GI infection, suggesting high virulence and release of fast-acting toxins. Farmers were more affected by the disease and thus it is an occupational disease. Clinical manifestations in patients were mostly in 2 forms of cutaneous (56.6%) and GI (42.83%) because of exposure to farm animals or soil and eating undercooked meat and liver of sheep or goats. Farmers were more infected because of exposure to herbivores and consuming their meat. Most of the cutaneous infections were on hands and faces of patients, showing the most available sites of the body for *B. anthracis* or spores contact. Moreover, among patients with GI infection, vomiting, abdominal pain, bloody stool and hemorrhage of upper and lower gastrointestinal tract were mostly observed. Studies on lethal toxin activity in laboratory animals have shown loss of plasma proteins, decreased platelet count, fibrin deposits in tissue sections, slower clotting times, and gross and histopathological sign of hemorrhage. Hemorrhage lead to disseminated intravascular coagulation and/or circulatory shock.[36] The cutaneous form is the most common mode of infection that causes a painless sore and if left untreated, may progress to septicaemia leading to a potentially lethal outcome in 20% of the cases.[37] In previous reports mentioned above, from 2000 to 2015, GI, cutaneous, eye infection and meningitis forms were detected, while no clinical report was found in 2016. An outbreak report of 28 cases of cutaneous form occurred in Esfarayen, Northeast Iran in 2011 where the livestock are more populated and this finding confirms the zoonotic risk of the disease as a most common route of infection transmission from herds. Several other reports from Northeast Iran show an endemic area.[18,38] Studies from human, sheep, cattle, goat and soil samples in several areas of Iran showed that all *B. anthracis* isolates were pXO1 (encoding toxins) and pXO2 (responsible for capsule synthesis) positive, emphasizing the presence of highly pathogenic strains countrywide.[17] Although the disease was affected by season and ecology conditions in China, we did not assess these conditions.[39] The mean of encapsulated pathogens from several other studies was 50.5%. Based on the results, it is necessary to plan for the prevention of 2 main forms of cutaneous and GI anthrax countrywide focusing on herds and farms. Moreover, there is a need for molecular typing of the strains causing outbreaks.

Conclusion

Cutaneous and GI forms are 2 main manifestations of anthrax in Iran. Although rare, anthrax continues to be a dreadful consequence of herds or soil exposure and consumption of undercooked meat of infected animals. Education plans and proper animal vaccination considering virulence factors are helpful in preventing the disease. Furthermore, rapid diagnosis of this infection is necessary because of the fast acting bacteria involved and also its fatal outcomes.

Ethical Approval

Not applicable.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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