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MAJOR ARTICLE

Variation in Tularemia Clinical Manifestations—Arkansas, 2009–2013

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Background. *Francisella tularensis*, although naturally occurring in Arkansas, is also a Tier 1 select agent and potential bioterrorism threat. As such, tularemia is nationally notifiable and mandatorily reported to the Arkansas Department of Health. We examined demographic and clinical characteristics among reported cases and outcomes to improve understanding of the epidemiology of tularemia in Arkansas.

Methods. Surveillance records on all tularemia cases investigated during 2009–2013 were reviewed.

Results. The analytic dataset was assembled from 284 tularemia reports, yielding 138 probable and confirmed tularemia cases during 2009–2013. Arthropod bite was identified in 77% of cases. Of 7 recognized tularemia manifestations, the typhoidal form was reported in 47% of cases, approximately double the proportion of the more classic manifestation, lymphadenopathy. Overall, 41% of patients were hospitalized; 3% died. The typhoidal form appeared to be more severe, accounting for the majority of sepsis and meningitis cases, hospitalizations, and deaths. Among patients with available antibiotic data, 88% received doxycycline and 12% received gentamicin.

Conclusions. Contrary to expectation, lymphadenopathy was not the most common manifestation observed in our registry. Instead, our patients were more likely to report only generalized typhoidal symptoms. Using lymphadenopathy as a primary symptom to initiate tularemia testing may be an insensitive diagnostic strategy and result in unrecognized cases. In endemic areas such as Arkansas, suspicion of tularemia should be high, especially during tick season. Outreach to clinicians describing the full range of presenting symptoms may help address misperceptions about tularemia.

Keywords. epidemiology; *Francisella tularensis*; manifestations; surveillance; tularemia.

Tularemia, caused by the highly pathogenic aerobic Gram-negative coccobacillus *Francisella tularensis*, is characterized as an acute, potentially fatal, febrile illness of humans and mammals, especially rabbits [1, 2]. *Francisella tularensis* is further subdivided into 4 subspecies, only 2 of which are truly pathogenic in humans as follows: *F tularensis* subspecies *tularensis*, referred to as Type A, and *F tularensis* subspecies *holarctica*, referred to as Type B. These 2 subspecies vary by geographic distribution and pathogenicity, with Type A, reported almost exclusively in North America, being the most virulent. Type B, also reported in North America, but more predominantly in Asia and Europe, appears to be less virulent in both humans and other mammals [2–6]. *Francisella tularensis* is capable of infecting hundreds of animal species, but disease is relatively uncommon in humans, except in endemic areas [3, 5].

Exposure usually occurs through direct contact with infected animals and their tissues, or arthropod bites, specifically ticks, deer flies, or other biting flies, and occasionally mosquitos (documented in Europe/Asia) [2–5]; however, exposure can also occur through contact with contaminated soil or ingestion of contaminated meats or water. Occasionally, exposure has occurred through direct cutaneous contact or inhalation of aerosolized organisms from agricultural, landscaping, or laboratory-associated activities [7, 8].

After the organism gains entry into its host, it is disseminated lymphohematogenously to the local lymph nodes and other organs and can lead to sepsis and death if not treated appropriately, although asymptomatic infection can also occur [3–5]. The incubation period for tularemia infection is typically 3–5 days, but it can be up to 21 days [2–5, 9].

Tularemia manifests as 1 of 7 recognized forms, dependent on inoculation route, host immune status, and extent of systemic involvement; however, these categories can overlap [3]. Classic tularemia is characterized by regional lymphadenopathy with or without skin or mucosal ulceration (ulceroglandular or glandular forms, respectively) [9]. This form has historically

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been confused with the "plague" in geographic areas of the world where *Yersinia pestis* is endemic [5]. Other forms are less common and occur when disease is isolated to particular organs or systems: eyes (oculoglandular), mouth and pharynx (oropharyngeal), intestinal tract (intestinal), or lungs (pneumonic) [10]. Each form is often characterized by sudden onset of influenza-like illness (ILI) symptoms, with varying degrees of chills, fever, headache, and myalgia. In the seventh form (typhoidal), ILI symptoms are the only symptoms described; no evidence of lymphadenopathy or localizing signs exists, and typically these patients are more severely ill [4, 5, 10, 12, 24]. Historically, this manifestation was a diagnosis of exclusion and less commonly reported than classic forms [10, 11]. Lymphohematogenous dissemination of the organism can lead to more severe disease forms, including meningitis, with the highest mortality [4, 9, 12]. The organism is highly infectious (infective dose: 10–50 organisms), easily aerosolized, potentially fatal, and historically has been incorporated into bioweapons; therefore, *F tularensis* is designated as a Tier 1 select agent, which makes public health surveillance imperative [13–15].

Tularemia is endemic in multiple states, but it is especially concentrated in Arkansas, Missouri, Oklahoma, and Kansas [14]. Tularemia, especially the typhoidal form, can mimic other summer ILI diseases in endemic regions (eg, spotted fever rickettsiosis, ehrlichiosis, West Nile virus, or enterovirus) and might not be considered by clinicians until classic, localizing symptoms appear [4–6]. Because tularemia is endemic in Arkansas, we believed that describing tularemia epidemiology and evaluating differences in presentation among exposure types, age groups, and manifestations were important. We also wanted to compare recent case investigation data with our historical understanding of tularemia in Arkansas.

METHODS

Case Definition and Study Design

Tularemia is reportable in the United States [15]. All confirmed and suspected tularemia cases are passively reported to the Arkansas Department of Health (ADH) by a wide variety of methods, including fax and electronic reporting, from laboratories, hospitals, and providers as required by state regulation. Investigations are initiated by ADH staff upon receipt of positive tularemia test results, and findings are documented by the investigator on the detailed Centers for Disease Control and Prevention (CDC) standardized Tularemia Case Investigation Report, which includes questions on medical history, symptoms, physical exam, radiographic and laboratory findings, clinical course and treatment, and epidemiologic and environmental exposures [16]. We performed a detailed retrospective case review and analysis of reports submitted to ADH during 2009–2013; when insufficient data were obtained from case reports, patient medical records were requested and examined. Using the 2010 Council of State and Territorial Epidemiologists Position Statement 09-ID-66 as our standard case definition [17], clinically compatible cases identified by either culture or a 4-fold antibody titer change between samples taken ≥2 weeks apart were characterized as confirmed. In contrast, cases with only 1 elevated titer, defined as ≥1:128 (microagglutination [MA]), or ≥1:160 (tube agglutination [TA]), or >15 U/mL (immunoglobulin [IgG/IgM] enzyme-linked immunosorbent assay [ELISA]), and tularemia-compatible symptoms, were classified as probable [3, 16–20]. The remaining suspect cases with limited clinical data and equivocal titers, defined as ≥1:64 but <1:128 MA, or ≥1:20 but <1:160 TA, or 10–15 U/mL ELISA and no subsequent available test results were excluded from our analysis. All serology results <1:64 MA, or <1:20 TA, or <10 U/mL ELISA were classified as not a case. Symptoms and physical findings reported from presentation and subsequent clinical findings during follow-up examinations were used to categorize cases into 1 of 7 clinical syndromes identified on the CDC Case Investigation Report (January 2006 version) [16]. All cases reporting no evidence of localized physical findings (skin ulcer, lymphadenopathy, pneumonia, etc) were classified as typhoidal; we further evaluated these cases for development of localizing symptoms during the course of their illness.

Study Oversight

The CDC reviewed this study for human subjects protection and determined it to be nonresearch. The Institutional Review Board (IRB) at the University of Arkansas for Medical Sciences determined the proposed work to be public health surveillance and not human subjects research (IRB no. 202114).

Statistical Analysis

Statistical analysis was performed by using Epi Info 7 (CDC, Atlanta, GA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA). Z-tests were used to assess differences between proportions, and statistical significance was defined as $P < .05$.

RESULTS

Study Population

During the 5 years from 2009 to 2013, ADH received 284 tularemia reports. Of these 284 reports submitted, 138 (49%) met the case definition for either confirmed (41, 30%) or probable (97, 70%) tularemia. At least 2 cases were previously identified tularemia cases. The remaining 146 (51%) did not meet the case definition. Among the noncases, 128 (88%) were excluded due to an alternative more likely diagnosis (113, 78%) or previous diagnosis of tularemia (15, 10%) with no evidence of current disease; 18 (12%) did not meet laboratory criteria.

The mean age of cases was 47 years (range, 1–83), and males were overrepresented at 67% (Figure 1). Eighty percent of patients were white, which is consistent with overall race demographics in Arkansas (78% white). Cases were reported from 37 (49%) of the counties in Arkansas, with the majority of cases clustered in northwest Arkansas; none were from the same household. Four cases were excluded due to insufficient clinical data.

Figure 1. Number of tularemia cases by sex and age group by decades—Arkansas, 2009–2013.

Reported Exposures

After being reported to ADH, all 284 patients were interviewed regarding potential exposures [16]; only exposure frequencies for 134 probable and confirmed cases are reported here. Arthropod exposure was by far the most common; 103 (77%) patients reported "tick, deerfly, or other biting fly bite" before symptom onset. Other sources reported in decreasing order of frequency included the following: exposure to "lawn mowing or landscaping" activity (43, 32%); "hunting, including contact with wild animals" (17, 13%); "contact with sick or dead animals" (12, 9%); "contact with or ingestion of soil or untreated water" (6, 4%); "contact with or ingestion of uncooked meat" (4, 3%); and working in a laboratory (1, 1%), although this was determined to be low-risk for tularemia because the worker was not involved in sample processing from ill patients. Both confirmed and probable cases demonstrated seasonality with the highest number of cases presenting during the summer months (Figure 2). No statistical correlations were found between routes of exposure and disease manifestations, and age groups by decade of age were not associated with exposure type.

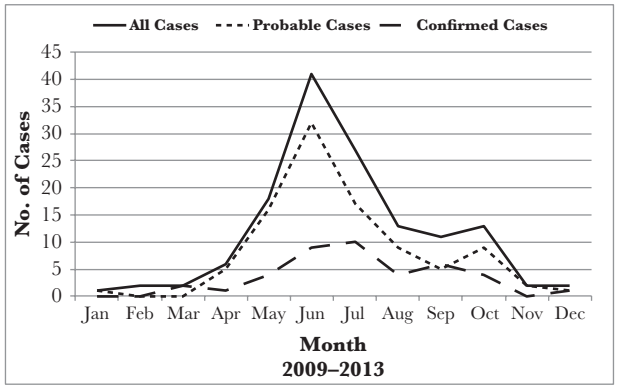

Figure 2. Combined total number of tularemia cases by month of presentation—Arkansas, 2009–2013.

Disease Manifestation

The mean number of days from symptom onset to serologic testing for 113 patients with serologic results was 19 (median = 9; range, 0–252); the mean number of days between samples was 34 (median = 28; range, 3–107) when 2 serologic samples were collected (n = 26).

When examining 134 confirmed and probable cases, 63 patients (47%) initially manifested as the typhoidal form. The ulceroglandular form was identified in 32 patients (24%), followed by 21 patients (16%) with glandular form, and other less commonly reported forms (Table 1). When we examined 39 confirmed cases alone to eliminate potential case-classification bias, we found a similar pattern with typhoidal manifestation identified most commonly in 18 patients (46%), followed by 13 patients (33%) with ulceroglandular, 4 patients (10%) with glandular, and other less commonly reported forms (Table 1).

When compared with other manifestations, the typhoidal form was more common among older age groups, whereas the lymphadenopathy forms were more equally represented among younger age groups. For 22 patients aged ≤17 years, 8 (36%) were typhoidal, 8 (36%) ulceroglandular, and 3 (14%) glandular. For 76 patients aged 18–64 years, 34 (45%) were typhoidal, 18 (24%) ulceroglandular, and 12 (16%) glandular. For 36 patients aged ≥65 years, 21 (58%) were typhoidal, 6 (17%) ulceroglandular, and 6 (17%) glandular (Figure 3).

Of note, a few typhoidal patients (9, 14%) converted to one of the more classic tularemia manifestations later during the course of their illness; however, the majority (54, 86%) remained typhoidal for illness duration. Of 9 typhoidal patients who converted, 4 patients (6%) eventually developed ulceroglandular lesions with a mean of 13 days (range, 5–30) after initial symptom onset, and 5 patients (8%) eventually developed glandular lesions with a mean of 30 days (range, 7–93) after onset. Considering these conversions, the final manifestation breakdown would be as follows: 54 (40%) typhoidal, 36 (27%) ulceroglandular, and 26 (19%) glandular.

Chest radiograph results were available for 54 patients (40%); 35 (65%) were patients that presented as typhoidal with no localizing signs or symptoms. None of these 35 patients had evidence of pulmonary infiltrates based on data relayed in their report or medical record; however, 1 patient subsequently developed pneumonia after noncompliance with antibiotic therapy.

Hospitalization occurred for 56 (42%) of all patients. Among 56 hospitalized patients, 22 (39%) were ≥60 years old and 3 (5%) reported underlying conditions (1 or more of the following: cardiovascular disease, renal disease, diabetes mellitus, cancer, and thrombocytopenia). All 9 patients with sepsis manifested initially as typhoidal; 8 (89%) were ≥60 years old. Of 5 patients with meningitis, 3 (60%) were ≥60 years old. Four of these manifested initially as typhoidal; 1 immunocompromised

Table 1. Manifestation of Tularemia by Case Status and Severity of Tularemia Manifestation by Hospitalization, Sepsis, Meningitis, and Death—Arkansas, 2009–2013[a]

Initial Manifestation	All Cases—Confirmed and Probable (n = 134)[b]	Confirmed Cases Only (n = 39)[b]	Hospitalization (n = 56)	Sepsis (n = 9)	Meningitis (n = 5)	Death (n = 4)
Typhoidal	63 (47)	18 (46)	28 (50)	9 (100)	4 (80)	3 (75)
Ulceroglandular	32 (24)	13 (33)	15 (27)	0	1 (20)	1 (25)
Glandular	21 (16)	4 (10)	6 (11)	0	0	0
Pneumonic	4 (3)	2 (5)	3 (5)	0	0	0
Intestinal	6 (4)	1 (3)	2 (3)	0	0	0
Oculoglandular	3 (2)	1 (3)	1 (2)	0	0	0
Oropharyngeal	5 (4)	0	1 (2)	0	0	0

[a]Values in parentheses refer to percentage. All percentages are calculated by column.

[b]Two probable and 2 confirmed cases omitted from this analysis due to insufficient clinical data.

patient with ulceroglandular tularemia ultimately developed meningitis as well. Overall, 4 deaths (3%) were identified; 3 were patients aged ≥60 years old, and all 4 reported underlying medical conditions (1 or more of the following: cardiovascular disease, renal disease, sickle cell anemia). Overall, typhoidal patients accounted for 50% of all hospitalizations and 3 of 4 deaths in our study (Table 1; Figure 4).

Antibiotic therapy was identified for 119 (89%) patients, 67 (56%) of which were treated with ≥2 antibiotics. Of those patients treated with antibiotics, doxycycline was prescribed most frequently for 106 patients (89%), gentamicin was prescribed for 14 (12%), and ciprofloxacin was prescribed for 9 (8%). Various other antibiotics, individually or in conjunction with those mentioned, were also used to treat patient illnesses. Two of 4 patients that died were treated initially with doxycycline or combination of doxycycline and clindamycin, whereas the other 2 patients that died were treated initially with a combination of doxycycline, vancomycin, and ceftriaxone, plus gentamicin and levofloxacin in 1 patient.

DISCUSSION

During 2009–2013, Arkansas had the highest tularemia incidence in the United States with rates 21 times greater than the national average, accounting for 18% of all US tularemia cases [21]. In Arkansas, 30% of cases were laboratory-confirmed; 70% were probable. This markedly differs from a report by Nelson et al [14] who determined that 64% of all cases in the United States from 2001 to 2010 were laboratory confirmed and 35% were probable. This difference might reflect varying testing practices over time or by regions.

In addition, the relative frequency of tularemia manifestations in our study differed from previous reports. Multiple

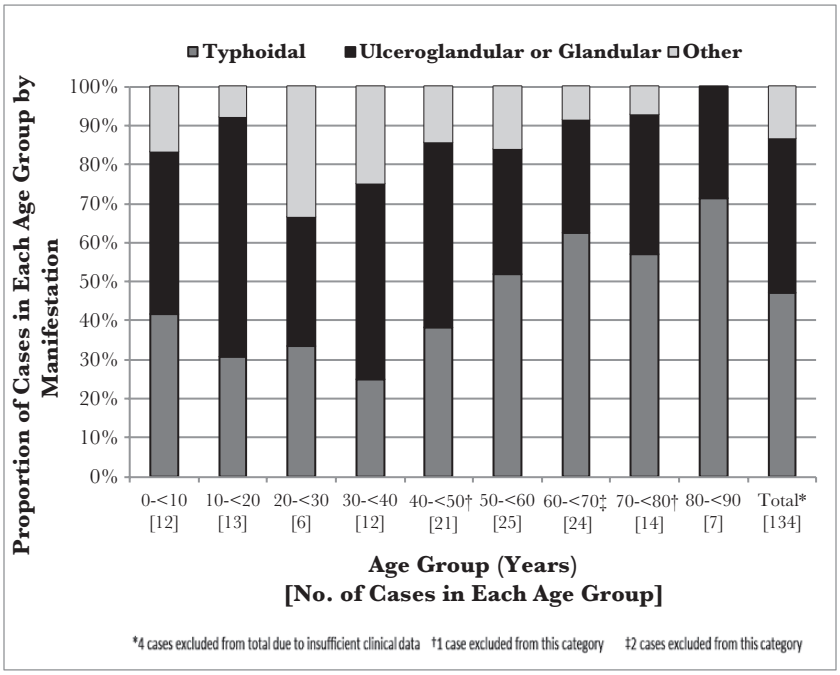

Figure 3. Proportion of tularemia cases by manifestation (typhoidal, ulceroglandular or glandular, or other) by decade of age—Arkansas, 2009–2013.

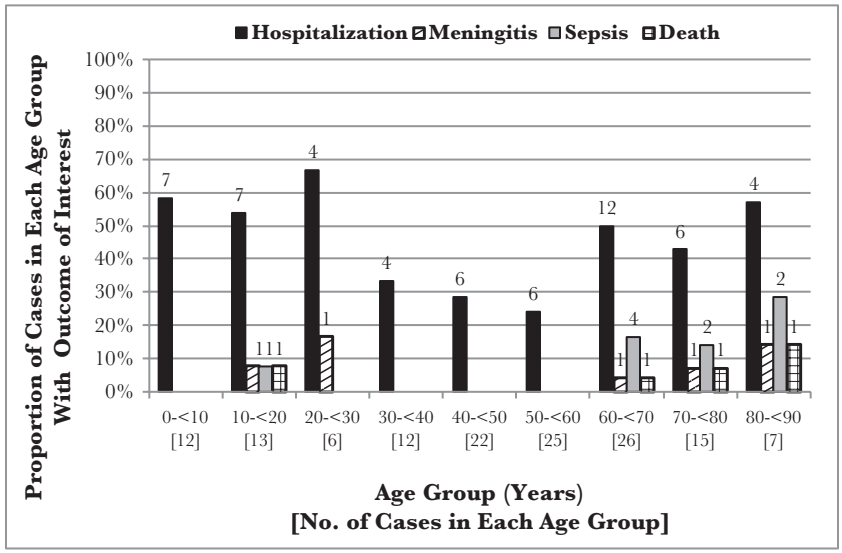

Figure 4. Outcome of tularemia by decade of age—Arkansas, 2009–2013.

sources reported that lymphadenopathy manifestations comprised the majority of cases, ranging from 21% to 85%, whereas the typhoidal manifestation was less commonly reported at 5%–30% [10–12, 18]. In 1983, Jacobs and Narain [1] reported that 51% of pediatric tularemia in Arkansas presented with lymphadenopathy; only 8% of cases were identified as typhoidal. When we looked at patients aged ≤17 years, we found a similar proportion of our pediatric cases (50%) were ulceroglandular or glandular, but we identified 4-fold higher proportion of cases as typhoidal (36% vs 8%) in the same area 30 years later. Weber et al [22] reported that 37% of tularemia manifestations in Missouri during 2000–2007 were ulceroglandular, 25% were glandular, and 10% were typhoidal. Our results were markedly different, with 24% ulceroglandular, 16% glandular, and 47% typhoidal. These differences might indicate improved awareness and testing methods, or they might reflect a change in the virulence of the organism not yet described.

Transmission mode was previously associated with manifestation type, particularly the correlation of arthropod bites with localized lymphadenopathy [5, 11, 14]. Our study indicated the majority of patients reported arthropod bites, but disease did not necessarily manifest grossly in the lymphatic system, instead it appeared to spread hematogenously without localizing signs in many cases. Otherwise, we might expect to see more lymphadenopathy in our study where 77% of the patients reported arthropods as a potential exposure source, but only 40% of patients were identified as having glandular enlargement. Unfortunately, we do not have a valid baseline tick exposure in Arkansas to differentiate tularemia cases reporting arthropod exposure from those cases unrelated to tularemia.

Tularemia manifestation might limit identification and reporting, which may be dependent on timing of presentation and testing in relation to disease progression. Our study appears to show evidence that most patients with nonlocalizing symptoms never progressed to localized disease for the duration of their illness. *Francisella tularensis* Type A is more commonly associated with typhoidal presentation, especially in those patients with compromised immune systems; this particular organism is prevalent in Arkansas and surrounding states [5, 6]. Therefore, clinicians in endemic regions may be more likely to treat typhoidal tularemia cases empirically for other tickborne diseases, foregoing definitive serology or blood cultures, resulting in underreported cases and potentially inappropriate case management. In contrast, patients with lymphadenopathy may be more inclined to seek prompt medical treatment, which may raise suspicion for tularemia, resulting in appropriate diagnostic testing and reporting. It is worth noting that tularemia can be geographically dynamic, and outbreaks have been historically identified in areas that are not considered endemic [7, 8, 23], so clinicians in these areas should remain vigilant about recognizing tularemia cases, which could occur due to a shift in either epidemiology or intentional use of *F tularensis*.

Aminoglycosides, specifically streptomycin and gentamicin, are the antibiotics of choice for successful tularemia treatment, especially in severe cases requiring hospitalization. Doxycycline and ciprofloxacin have been used with limited success, mostly in milder cases, although fluoroquinolones are currently considered to be more effective than tetracyclines [2, 4, 5, 12, 25]. Penn [3] reported overall death rates from tularemia in the antibiotic era have been ≤4%, but these rates had been as high as 60% before introduction of streptomycin as treatment; our death rate was similar at 3%. Although it is not the preferred first-line tularemia antibiotic, 67% of study patients received doxycycline initially, whereas far fewer patients received gentamicin, presumably as an adjunctive treatment after doxycycline failure or

tularemia confirmation; streptomycin therapy was not reported in our study. Tickborne diseases, including spotted fever rickettsiosis, ehrlichiosis, and anaplasmosis, are endemic in Arkansas [26–28], and clinicians routinely treat symptomatic patients with doxycycline empirically during tick season. In addition, because aminoglycosides are less broad spectrum and require parenteral administration, they might not be considered initially until the differential diagnosis suggests a disease that is amenable to their administration or after failed oral antibiotic therapy. Our treatment data were limited and did not allow for correlation among illness onset, severity, treatment delay, and relapses.

This was a descriptive epidemiologic study using retrospective data collected for surveillance purposes, so limitations exist. Although Arkansas may have 1 of the most robust tularemia datasets in the nation, rarity of tularemia makes subgrouped or other more sophisticated analyses difficult to conduct. The case definition for probable tularemia is nonspecific and open to interpretation, creating difficulties for surveillance staff to apply uniformly, even within the same health department. Finally, our findings might be novel in that they differ from what has been historically reported; this may be due, in part, to how we classified cases based on initial presentation compared with how it was done in the past.

CONCLUSIONS

Higher tularemia suspicion in Arkansas might promote enhanced case reporting of persons with milder symptoms or nonspecific constitutional signs, compared with areas where tularemia is less prevalent. Because tularemia patients can present with only nonlocalizing typhoidal symptoms, we believe that using lymphadenopathy as a necessary feature to initiate tularemia testing might delay case recognition or even possibly an outbreak. It might also delay opportunities to initiate presumptive treatment of patients during earlier infection stages before disease progresses in severity. The medical community, especially in tularemia endemic regions, should be aware of the variation of tularemia presentations and consider typhoidal tularemia in patients lacking localizing symptoms. In particular, we believe it is important to remind clinicians that tularemia patients do not always present initially with classic signs and can demonstrate manifestations that may change throughout the course of their illness.

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