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BRIEF REPORT

Anaplasmosis in Pennsylvania: Clinical Features, Diagnosis, and Outcomes of Patients Diagnosed With *Anaplasma phagocytophilum* Infection at Hershey Medical Center From 2008 to 2021

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Anaplasmosis is an emerging infection in the United States and in particular, Pennsylvania. We highlight the abrupt rise in cases of anaplasmosis in the past decade in the state of Pennsylvania with the hope of increasing clinician awareness. We identified a cohort of 61 patients diagnosed with anaplasmosis at our institution as well as cases reported to the Department of Health. From our review, we identified not only an increase in cases over time but what appears to be an expansion further into central and western Pennsylvania over time.

Keywords. *anaplasma*; anaplasmosis; Pennsylvania, United States; tick-borne diseases.

Human granulocytic anaplasmosis (HGA), a tick-borne disease caused by the gram-negative bacterium *Anaplasma phagocytophilum*, has been identified as an emerging infection with a rapidly increasing incidence in the United States (US) [1–3]. The primary route of transmission is via tick bite, with the majority of human cases occurring in the northeastern and upper midwestern US. *Ixodes scapularis* (blacklegged tick) serves as the primary vector in the northeast and midwest states, *Ixodes pacificus* as the key vector in the western US, and *Ixodes ricinus* in most of Europe [4]. There have also been rare reports of transmission via blood products and organ transplantation [5–8]. The primary reservoirs are the white-tailed deer and the white-footed mouse. Most cases of anaplasmosis are seen during the summer months, with a peak in June and July [9].

Anaplasmosis became nationally notifiable in 1999 and is a mandatory reportable infection in Pennsylvania. Data obtained from the Centers for Disease Control and Prevention (CDC) show an approximately 15-fold increase in the incidence of anaplasmosis cases, from 348 cases in 2000 to 5655 cases in 2019 [10]. There has also been evidence of a sharp rise in cases in the US state of Pennsylvania [11]. We have suspected a similar surge of cases at our institution, Penn State, Milton S. Hershey Medical Center (Hershey, Pennsylvania), which is a tertiary academic center located in central Pennsylvania. We performed a retrospective review of all of the cases of anaplasmosis at our institution from 2008 through 2021. We sought to identify whether we were truly seeing an increase in the number of cases of anaplasmosis and to highlight the demographic and clinical characteristics of these patients. We also sought to review data from our hospital and the Department of Health (DOH) to better describe this rise, specifically identifying when it began and any unique geographical characteristics associated with the increase.

METHODS

After institutional review board approval, we obtained a list of patients at Hershey Medical Center who had *International Classification of Diseases, Ninth* or *Tenth Revision* codes for anaplasmosis and diagnosis codes for anaplasmosis serology from 2008 through 2021. According to data from the PA DOH, the first reported anaplasmosis case in southcentral Pennsylvania counties (the primary catchment area for Hershey Medical Center) was in 2013. To ensure we did not miss any cases in the years preceding 2013, we expanded our search from 2008 to 2021. We then performed a retrospective chart review to identify cases that met criteria for the diagnosis of anaplasmosis. We used the CDC criteria to identify our cases [12]. This included both confirmed and probable cases and is consistent with what is considered reportable to the DOH. To meet the case definition, patients required both clinical and laboratory evidence of infection. Criteria for clinical evidence included fever and at least 1 of the following: headache, myalgia, malaise, anemia, leukopenia, thrombocytopenia, or elevated hepatic aminotransferases. Laboratory evidence needed to be supportive or confirmatory. Supportive evidence included serological evidence of elevated immunoglobulin G (IgG) titers or visualization of morulae in the cytoplasm of neutrophils or eosinophils by microscopic examination. Confirmatory evidence included serological evidence of at least a 4-fold change in IgG titer by indirect immunofluorescence assay in paired serum

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samples (acute and convalescent samples) or by detection of DNA by polymerase chain reaction (PCR) assay. Confirmed cases had clinical evidence of infection and confirmatory laboratory evidence. Probable cases had clinical evidence of infection and supportive laboratory evidence. Only cases meeting the definition of either confirmed or probable were included in our study. Using these criteria, we identified a total of 61 patients.

RESULTS

Table 1 provides a summary of the demographics and clinical characteristics of the patients diagnosed with anaplasmosis at Hershey Medical Center from 2008 through 2021. The majority of patients were >60 years of age (77%) with a median age of 68 (range, 18–96 years). Fifty-six percent were male, with 24 patients (39%) recalling history of recent tick bite and 49 (80%) reporting outdoor activity preceding their illness. None of the patients reported recent blood transfusion. The majority of the patients presented during the summer months of May–July (37 patients [~61%]). The highest number of cases was in June (20 [~33% of the cases]). Outside of the May–July timeframe, the second highest months were the months of November (7 cases) and December (5 cases).

The first case identified at Hershey Medical Center was in 2013, followed by a notable rise in cases starting in 2017, with sustained cases in the double digits since 2018. We see a similar trend when looking at cases reported to the Pennsylvania DOH over that same time period. 2013 marks the first year with double-digit cases, followed by case numbers in the triple digits since 2019. Case numbers in 2021 were >600. As illustrated in Figure 1, we identified not only an increase in cases over time, but also what appears to be an expansion further into central and western Pennsylvania over time when looking at breakdown of cases per county per year.

The most common presenting symptoms were subjective fever (85%); fatigue (77%); gastrointestinal (GI) symptoms with nausea, vomiting, diarrhea, abdominal pain, or anorexia (64%); myalgias/arthralgias (56%); and headache (43%). Rash was present in 15% of patients. The laboratory abnormalities most frequently identified included transaminitis (71%), thrombocytopenia (69%), anemia (39%), and leukopenia (27%). Diagnosis was made through PCR testing, blood smears, and/or serology. All patients had serology obtained, with approximately 70% having positive results. A total of 47 patients had blood smears obtained, with only 21% of smears being positive. Of the 26 patients who underwent PCR testing, 100% had positive results. Upon further review of the patients with positive PCR testing, we identified that 33% of the patients with positive PCR testing had negative blood smears, 23% had negative serology, and 23% had both negative smear and serology testing.

All but 1 patient survived, and reported complications included respiratory failure (13%), shock (8%), acute kidney injury (25%), hemophagocytic lymphohistiocytosis (2 patients), and disseminated intravascular coagulation (1 patient). Patients who experienced complications were older, with an average age of 77 years. All patients but 1 were treated with doxycycline. More than half (62%) received infectious disease

Table 1. Demographics, Clinical Characteristics, Symptoms, and Laboratories of Patients With Anaplasmosis

Characteristic	No. (%)
Age at presentation, y	
18–60	15 (24.6)
≥60	46 (75.4)
Sex	
Male	34 (55.7)
Female	27 (44.3)
Month infection acquired	
January–April	5 (8.2)
May–August	40 (65.6)
September–December	16 (26.2)
History of tick bite	24 (39.3)
History of outdoor activity	49 (80)
History of blood transfusion	0
Comorbidities	
Diabetes	7 (11.5)
Chronic kidney disease	7 (11.5)
Hypertension	19 (31.1)
Immunosuppressive therapy	5 (8.2)
Solid organ transplant	2 (3.3)
Symptoms	
Fever	52 (85.2)
Fatigue	47 (77)
Chills	32 (52.5)
Headache	26 (42.6)
Myalgias/arthralgias	34 (55.7)
GI symptoms (nausea, vomiting, diarrhea, abdominal pain, or anorexia)	39 (63.9)
Rash	9 (14.8)
Laboratory tests, average	
Hemoglobin, g/dL	12.7
WBC, $\times 10^9$/L	5.7
Platelets, $\times 10^9$/L	111
ALT, U/L	73
AST, U/L	102
Creatinine, mg/dL	1.7
Complications	
Respiratory failure	8 (13.1)
Shock	5 (8.2)
AKI	15 (24.6)
HLH	2 (3.3)
DIC	1 (1.6)
Coinfection	
Lyme	8 (13.1)
Babesia	2 (3.3)
ID consult	38 (62.3)
Treatment with doxycycline	60 (98.3)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulation; GI, gastrointestinal; HLH, hemophagocytic lymphohistiocytosis; ID, infectious diseases; WBC, white blood cell count.

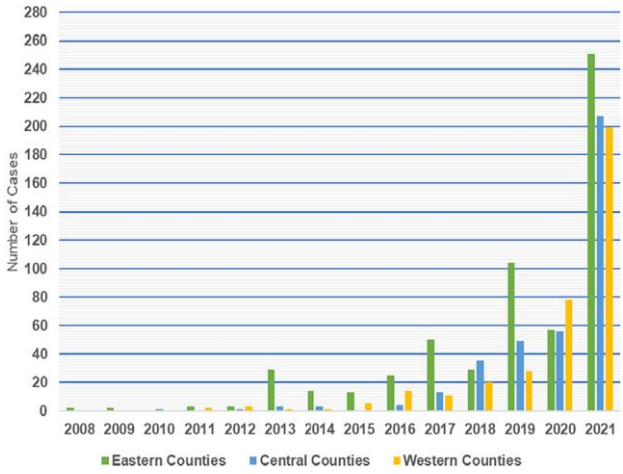

Figure 1. Anaplasma cases in Pennsylvania by region, 2008–2021.

consultations. Eight patients (13%) had Lyme coinfection and 2 (3%) had *Babesia* coinfection.

DISCUSSION

From the review of cases seen at our institution and evaluating data from the DOH, it is clear that anaplasmosis is an emerging and now most likely endemic infection in Pennsylvania. There is not only evidence of a rise in the number of human infections, but as expected, state data show increasing tick infection rates as well. Tick infection rates for *Anaplasma phagocytophilum* in Pennsylvania during 2012–2014 were approximately 3.3% compared to more recent data from the Department of Environmental Protection reporting rates of 10%–12% [13]. This increase is thought to be in part from improved awareness from clinicians and the general public regarding anaplasmosis. In addition, continued climate change has been postulated as having an effect on increasing numbers of tick vectors and mammalian hosts [2,14], with both a rise in the number of ticks and further human incursion into tick and deer habitats surely playing a role. As previously highlighted in Figure 1, the distribution of cases over time suggests an expansion of anaplasmosis further into central and western Pennsylvania. A similar pattern was seen in a publication highlighting cases of babesiosis in Pennsylvania [15]. It is worth noting that this sharp increase in number of cases at our institution may be due (at least partially) to an increase in testing being performed. However, we believe this is an overall reflection of a true rise in cases given we also identified an increase in number of cases reported throughout the state to the DOH as well as an increase in the number of ticks infected with *Anaplasma* over time.

Similar to other studies, the majority of our patients were older, with 77% being aged >60 years. Only 39% recalled a history of tick bite, but the majority (~80%) did report some outdoor activity preceding their illness. Symptoms are more common in older age and infection may be mild or even asymptomatic in young healthy individuals [4]. We suspect that this larger percentage of older patients being diagnosed is due to a higher likelihood of having symptoms severe enough to prompt further evaluation and testing. As expected, most cases were during the summer months, but it is worth highlighting that the second highest number of cases outside of May–July occurred during November–December. This second peak in the fall/winter is important for clinicians to recognize, given that it falls outside of typical tick season.

Anaplasmosis often presents as a nonspecific febrile illness. Interestingly, in our study, outside of fever and fatigue, GI symptoms were the most common presenting symptom with 64% of the patients presenting with nausea, vomiting, diarrhea, abdominal pain, or anorexia. This is higher than most prior studies, but a recent systematic review of published cases of anaplasmosis identified that 55.5% of the patients presented with GI symptoms [16]. We also identified rash as a presenting symptom in 15% of patients. We did not identify clinical features that were unique to a specific time of year/season.

Given the nonspecific nature of presentation, diagnosis can be a challenge. PCR testing, with high sensitivity and specificity, is the most effective diagnostic test [17,18]. All of our patients who had PCR testing obtained had positive results. Of those PCR-positive patients, 33% had negative blood smears, 23% had negative serology, and 23% had both negative smear and serology testing. These findings emphasized the importance of pursuing PCR testing in cases of high clinical suspicion even with negative blood smears or serology. Furthermore, a negative blood smear or negative serology should not rule out diagnosis.

CONCLUSIONS

Clinicians need to be made aware of the rapidly rising incidence of anaplasmosis in the state of Pennsylvania. Infection can occur outside of peak tick season, with cases in the months of October–December. GI symptoms may be a more frequent presenting symptom with HGA infection. Negative blood smear or serology does not rule out diagnosis, but if clinical suspicion is high, PCR testing should be obtained.

Notes

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Patient consent. This study was reviewed and approved by our institutional review board. It was determined that our retrospective study does not necessitate patient consent.

Potential conflicts of interest. All authors: no reported conflicts.

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