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Human ehrlichiosis at a tertiary-care academic medical center: Clinical associations and outcomes of transplant patients and patients with hemophagocytic lymphohistiocytosis

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ABSTRACT

Background: Ehrlichiosis is an acute febrile tick-borne disease which can rarely be a trigger for secondary hemophagocytic lymphohistiocytosis (HLH).
Methods: We reviewed our experience with *Ehrlichia* infections at a tertiary-care academic medical center.
Results: Over 10 years, 157 cases of ehrlichiosis were identified. Ten patients (6.4%) had infection with *E. ewingii*, 7(4.5%) of whom were transplant patients as compared to 3(1.9%) non-transplant patients (p = .035). Transplant patients were more likely to have leukopenia and elevated creatinine compared to immunocompetent patients; length of hospital stay and early mortality were not different between the two groups. Ten patients met the HLH-2004 diagnosis criteria, which could be an underestimation of HLH occurrence as most patients were not completely evaluated for these criteria. We calculated the H-Score to find the probability of HLH; 25 patients scored high making the occurrence rate of HLH at least 16%. *Ehrlichia*-induced HLH patients (N = 25) had more anemia, thrombocytopenia, elevated creatinine and AST. Moreover, they had a significantly longer hospital stay (median 9 days) compared to patients without HLH (median 4 days) (p = .006).
Conclusions: *Ehrlichia*-induced HLH is a potential serious complication with relatively high occurrence rate; patients manifest severe disease with end-organ damage requiring longer hospital stay.

1. Introduction

Ehrlichiosis is a general term used to describe an acute febrile tick-borne disease caused by members of the genera *Ehrlichia* and *Anaplasma*. Most of these infections affecting humans are caused by three distinct species: *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and *Anaplasma phagocytophilum* [1,2]. *Ehrlichia chaffeensis* and *Ehrlichia ewingii* are obligate intracellular bacteria that infect monocytes and cause human monocytotropic (monocytic) ehrlichiosis (HME). Both are transmitted through the bite of the Lone Star tick (*Amblyomma americanum*) which occurs across the south-central and southeastern states [3]. The white-tailed deer *Odocoileus virginianus* is the primary host of the Lone Star tick.

Ehrlichiosis is usually seasonal with the majority of cases occurring during spring and summer seasons. Patients may present with fever, chills, headache, cough, and rash [4]. In addition, patients may have leukopenia, thrombocytopenia, and elevated liver enzymes [5]. The clinical course can be severe especially in subjects with impaired immune function including solid organ and stem cell transplant patients [6–9]. Lung transplant patients tend to have a more severe illness [8]. In addition, *Ehrlichia* can be a trigger for secondary hemophagocytic lymphohistiocytosis (HLH) [10,11], which is a potentially fatal syndrome characterized by an uncontrolled hyperinflammatory response.

We reviewed our experience with *Ehrlichia* infections to 1) evaluate the clinical outcomes in transplant patients and compare them with non-transplant patients, and to 2) determine the occurrence rate of HLH among patients diagnosed with *Ehrlichia*.

2. Methods

This retrospective chart review study was approved by the Institutional Review Board at Washington University School of Medicine in St. Louis. Patients diagnosed with ehrlichiosis from May 2007 to October 2016 at Barnes-Jewish Hospital in St. Louis, Missouri, were identified using the hospital's laboratory information system. We reviewed clinical and laboratory data from the patients' medical

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records. Patients were classified into two study groups based on their history of organ transplant: transplant patients versus non-transplant patients. The group of transplant patients included recipients of solid organ transplant or allogeneic stem cell transplants on immunosuppressive medications.

We evaluated the reviewed cases for clinical and laboratory findings of HLH. The criteria of the 2004 Histiocyte Society for HLH diagnosis were followed to establish a diagnosis of HLH (HLH-2004) [12]. HLH-2004 criteria requires for a diagnosis of HLH either a molecular diagnosis consistent with HLH, or meeting five of the following eight criteria: 1) fever ≥38.5 °C; 2) splenomegaly; 3) cytopenia of two or three lines: absolute neutrophil count (ANC) < 1×10^9/L, hemoglobin < 9 g/dL, platelet count < 100×10^9/L; 4) hypertriglyceridemia ≥265 mg/dL or hypofibrinogenemia ≤150 mg/dL; 5) serum ferritin ≥500 μg/L; 6) soluble IL-2 receptor (i.e. soluble CD25) ≥2400 U/mL; 7) low or absent NK cell activity; and 8) pathology showing hemophagocytosis (bone marrow, spleen, lymph nodes, or liver).

The majority of patients were not actively evaluated for all HLH-2004 diagnostic criteria, thus it was impossible to rule out HLH on many patients. To estimate the occurrence rate of *Ehrlichia*-induced HLH we calculated the H-Score which corresponds to a set of weighted criteria that are more commonly available allowing effective estimation of patient's risk of having HLH (Table 1) [13]. According to Fardet and colleagues, a cutoff of > 169 points was considered optimal for HLH diagnosis which corresponded to a sensitivity of 93%, a specificity of 86%, and accuracy of 90%. H-Score was calculated using a freely available online link (http://saintantoine.aphp.fr/score/).

We only included patients with confirmed diagnosis of *Ehrlichia* (based upon a positive PCR assay performed on whole blood) who were admitted to our medical center for management. The diagnosis of *Ehrlichia* was made by polymerase chain reaction (PCR) testing on peripheral blood with or without cerebral spinal fluid (CSF) testing [2].

Table 1
The H-Score: parameters and their assigned points.[a]

Parameter	Available criteria	No. of points
Known underlying immunosuppression[b]	No	0
	Yes	18
Temperature (°C)	< 38.4	0
	38.4–39.4	33
	> 39.4	49
Organomegaly	No hepatomegaly or splenomegaly	0
	Hepatomegaly or splenomegaly	23
	Hepatomegaly and splenomegaly	38
No. of cytopenias[c]	1 lineage	0
	2 lineages	24
	3 lineages	34
Ferritin (ng/ml)	< 2000	0
	2000–6000	35
	> 6000	50
Triglyceride (mmoles/l)	< 1.5	0
	1.5–4	44
	> 4	64
Fibrinogen (g/l)	> 2.5	0
	≤2.5	30
SGOT (IU/l)	< 30	0
	≥30	19
Hemophagocytosis on BM	No	0
	Yes	35

Abbreviations: SGOT, serum glutamic oxaloacetic transaminase; BM, bone marrow.

[a] Reprinted with permission from John Wiley & Sons, Inc. [13].

[b] Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine).

[c] Defined as hemoglobin level of ≤9.2 g/dL and/or a leukocyte count of ≤5000/mm^3 and/or a platelet count of ≤110,000/mm^3.

Table 2
Demographic characteristics of patients with *Ehrlichia* infection.

	Transplant (N = 56)	Immunocompetent (N = 101)	p-Value
Age, median (range), years	56.9 (9–72)	47.6 (1–91)	0.004
Gender, N (%)			
Male	42 (26.8)	56 (35.7)	0.015
Female	14 (8.9)	45 (28.6)	
Race, N (%)			
White	55 (35)	95 (60.6)	NS
Black	1 (0.6)	6 (3.8)	
History of tick exposure, N (%)			
Yes	37 (23.6)	54 (34.4)	NS
No	19 (12.1)	47 (29.9)	
Ehrlichia species, N (%)			
E. chaffeensis	49 (31.2)	98 (62.4)	0.035
E. ewingii	7 (4.5)	3 (1.9)	
Organ of transplant, N (%)			
Kidney	18 (32.1)	NA	
Heart	12 (21.4)		
Lung	12 (21.4)		
Liver	7 (12.5)		
Kidney and pancreas	2 (3.6)		
Allogeneic stem cells	5 (9)		

Abbreviations: NA: not applicable; NS: not significant.

2.1. Statistical analysis

Collected data was entered into a computer dataset, and statistical analyses were performed using SPSS (Statistical Package for Social Sciences) software, version 22 (SPSS Inc., Chicago, IL, USA). Results were presented as median plus range or percentages as indicated. All the investigated variables were analyzed statistically using Student's *t*-test, the Pearson's Chi-square test, and Fisher's exact test. p values < .05 were considered statistically significant.

3. Results

From May 2007 to October 2016, 157 cases of ehrlichiosis were identified and managed at our institution. The majority of patients were Caucasian and 62% were male. The demographic characteristics on the transplant and immunocompetent patients are presented in Table 2. There was a significant difference in age and gender between the two groups. The medical records of patients documented tick exposure/bites in 58% of cases. *E. chaffeensis* was the most common species identified (93.6%). Ten patients (6.4%) had infection with *E. ewingii*, 7 (4.5%) of whom were transplant patients as compared to 3 (1.9%) non-transplant patients (p = .035). Among the 56 transplant patients, 51 (91%) were solid organ transplant recipients and 5 (9%) received allogeneic stem cell grafts. Fig. 1 shows the monthly distribution of *Ehrlichia* infections between the two groups of patients. As expected, most infections were diagnosed during the spring and summer seasons, with 87% of cases presenting during May through August. Fig. 2 shows the yearly distribution of *Ehrlichia* infections between the two groups of patients.

3.1. Laboratory data/outcome

Laboratory data at presentation are summarized in Table 3. There was a significant difference in the white blood cell count between the two groups with transplant patients having more leukopenia compared to immunocompetent patients (p = .034). In blood chemistries, serum sodium was lower and creatinine was higher in the transplant group.

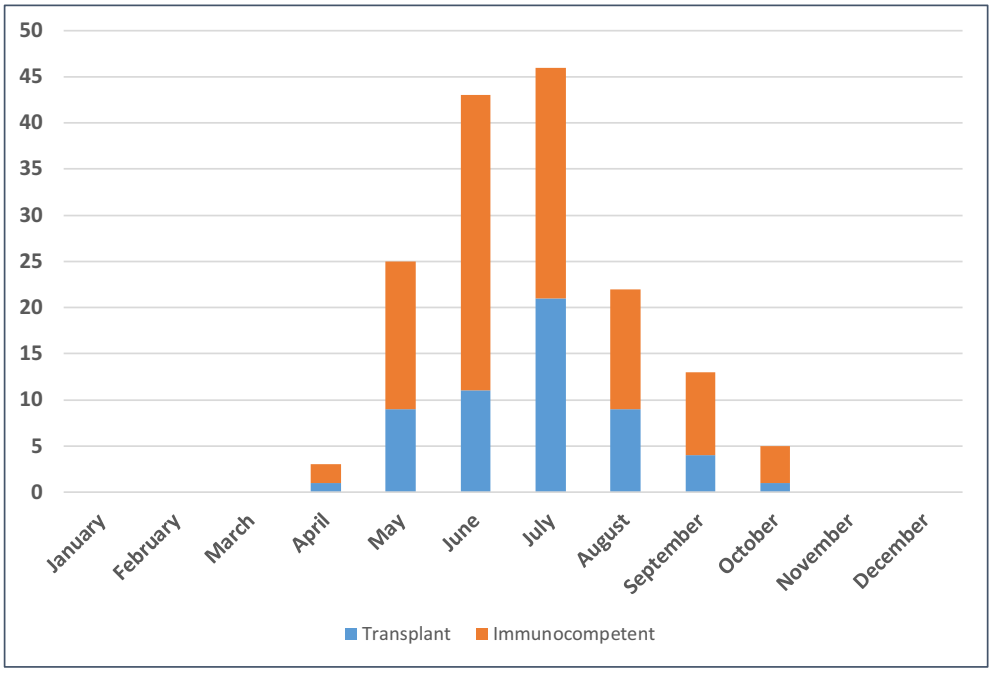

Fig. 1. Monthly distribution of *Ehrlichia* infection.

Serum albumin was higher in transplant patients. There was no significant difference in coagulation parameters between the two groups. There was a significant difference in alkaline phosphatase levels (85.5 versus 124 IU/L; p = .004) between transplant patients and immunocompetent patients.

The median length of hospital stay was 5 days (range: 1–30 days) for transplant patients and 4 days (range: 1–29 days) for immunocompetent patients (p = .675). Only 2 patients died during hospital stay (at 6 and 15 days) from end organ failure and septic shock; both were immunocompetent patients. Twelve (7.6%) patients had CNS involvement; none of them died during admission and only two of these patients were transplant patients.

3.2. Ehrlichia-induced HLH (as determined by HLH-2004 diagnostic criteria)

Table 4 summarizes the initial characteristics of patients with *Ehrlichia*-induced HLH. We identified 10 patients who met the criteria for HLH diagnosis. *Ehrlichia* was the only identified trigger for HLH in these patients. Genetic testing was performed only on Patients 4 and 6 and was negative for familial HLH. All patients were Caucasian with a median age of 30.7 years (range: 7–76 years). All patients had fever, cytopenias, and high ferritin levels. The median ferritin level was 40,189 μg/L (range: 2863–85,517 μg/L). Bone marrow biopsy was performed on 5 patients, and 4 showed hemophagocytosis. Only one patient (Patient 5) was a transplant patient who received bilateral lung

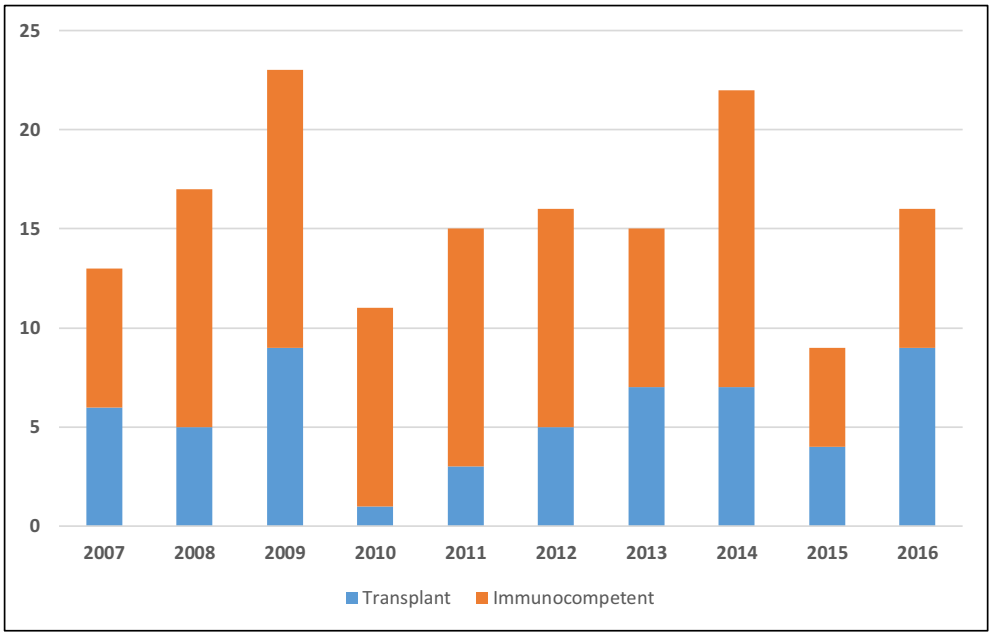

Fig. 2. Yearly distribution of *Ehrlichia* infection.

Table 3
Patients' laboratory data at initial presentation comparing transplant versus non-transplant patients (values are presented as medians with ranges in parentheses).

Blood test	Transplant (N = 56)	Immunocompetent (N = 101)	p-Value
WBC count ($\times 10^3$/μL)	2.9 (0.5–18.8)	3.1 (0.4–39)	0.034
Hemoglobin (g/dL)	11.2 (6.1–17.3)	10.8 (7–15.1)	NS
Platelets ($\times 10^3$/μL)	61.5 (15–225)	61 (3–454)	NS
Serum sodium (mEq/L)	132 (118–142)	134 (120–156)	0.009
Serum creatinine (mg/dL)	1.76 (0.4–8.17)	0.96 (0.3–6.2)	< 0.001
BUN (mg/dL)	31 (10–83)	16 (3–85)	0.001
PT (s)	14.5 (9.8–33.7)	15 (9.7–103)	NS
PTT (s)	38.4 (24.3–74.4)	41 (4.6–187)	NS
Serum protein (g/dL)	5.9 (4.5–7.9)	5.6 (4.2–7.7)	NS
Serum albumin (g/dL)	3.2 (2.2–4.5)	3 (2–4.8)	0.017
Alkaline phosphatase (IU/L)	85.5 (33–493)	124 (24–586)	0.004
AST (IU/L)	111 (16–1267)	133 (17–3680)	NS
ALT (IU/L)	72 (16–1264)	101 (19–1269)	NS
LDH (IU/L)	392 (149–1840)	565 (208–6860)	NS

Abbreviations: WBC: white blood cell; BUN: blood urea nitrogen; PT: prothrombin time; PTT: partial thromboplastin time; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; NS: not significant.

grafts. Two patients with neurologic symptoms tested positive for *E. chaffeensis* in CSF. Only one patient (Patient 8) died from septic shock 15 days from admission. Interestingly, one patient (Patient 6) had an early relapse of HLH with recurrent *Ehrlichia* infection 6 weeks after initial presentation which was treated with doxycycline and HLH-94 protocol. All other patients responded well to treatment with no recurrence of HLH after a median follow up of 10.7 months.

3.3. Ehrlichia-induced HLH (as determined by H-Score probability)

We sought to estimate the occurrence rate of *Ehrlichia*-induced HLH among our patient cohort. Table 5 summarizes the breakdown of the available diagnostic criteria of patients. Only 10 patients fulfilled the HLH-2004 diagnostic criteria; however, only 52/157 patients were tested for at least 5 of the criteria which makes it difficult to rule out HLH in the majority of patient. The H-Score was calculated using the online link; 25 patients scored > 169. This makes the occurrence rate of HLH at least 16% (25/157). All patients who fulfilled the HLH-2004 criteria scored > 169 in the H-Score. Table 6 summarizes the laboratory data of *Ehrlichia*-induced HLH patients (determined by H-Score probability) as compared to non HLH patients. *Ehrlichia*-induced HLH patients were more likely to have anemia, thrombocytopenia, elevated creatinine, LDH and AST compared to non HLH patients. In addition, *Ehrlichia*-induced HLH patients had a significantly longer hospital stay (median 9 days; range 1–29 days) than patients without HLH (median 4 days; range: 1–30 days) (p = .006). One patient from each group died during hospital stay.

Table 5
Breakdown of cases and the available diagnostic criteria.

No. of patients	HLH-2004 diagnostic criteria		HLH diagnosis or probability
	No. of met criteria	No. of available or tested criteria	
1	7	8	HLH, High H-Score
2	6	7	HLH, High H-Score
3	5	7	HLH, High H-Score
3	5	6	HLH, High H-Score
1	5	5	HLH, High H-Score
4	4	6	High H-Score in 3 patients
12	4	5	High H-Score in 8 patients
5	4	4	
1	3	6	
18	3	5	High H-Score in 4 patients
10	3	4	
4	3	3	
7	2	5	
6	2	4	
16	2	3	
18	1	4	
26	1	3	
Total: 157			Total: 25

4. Discussion

Human monocytotropic ehrlichiosis (HME) is the most common form of ehrlichiosis in the south-central and southeastern regions of the United States and is mostly caused by *E. chaffeensis* [3]. Ehrlichiosis can be severe with up to 49% of cases requiring hospitalization [14]. Presumptive diagnosis is based primarily on clinical suspicion and non-specific signs, symptoms, and laboratory findings. Serum antibodies are detectable in a small percentage of patients, thus PCR has become the diagnostic test for acute ehrlichiosis [15,16]. Prognosis is better if

Table 4
Clinical and laboratory values of patients with *Ehrlichia*-induced HLH (HLH-2004 criteria met).

Characteristic	Pt #1[a]	Pt #2[a]	Pt #3	Pt #4	Pt #5	Pt #6	Pt #7	Pt #8	Pt #9	Pt #10
Age (years)	52	47	59	16	62	9	7	77	11	7
Gender	F	F	F	F	M	F	F	M	M	F
Fever	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Splenomegaly	N	N	N	N	**Y**	N	**Y**	N	N	N
ANC ($\times 10^3$/μL)	**0.1**	12.1	**0.6**	**0.4**	3.9	**0.5**	N/A	1.7	**0.8**	N/A
Hemoglobin (g/dL)	**7.9**	**8.6**	10.6	11.9	**8.8**	10.2	**8.4**	**7.55**	9.9	**7.9**
Platelets ($\times 10^3$/μL)	**25**	**65**	**41**	**37**	**20**	**28**	**51**	**40**	**15**	**44**
Triglycerides (mg/dL)	**650**	**710**	**307**	**319**	**516**	**314**	**401**	**700**	**340**	126
Fibrinogen (mg/dL)	173	178	N/P	187	312	**138**	253	192	159	**93**
Ferritin (μg/L)	**47,290**	**10,002**	**2863**	**85,517**	**84,676**	**36,282**	**3183**	**79,101**	**21,187**	**44,095**
Hemophagocytosis	**Y**	N	**Y**	**Y**	N/P	**Y**	N/P	N/P	N/P	N/P
Soluble IL-2 receptor (U/mL)	**> 6500**	**5873**	N/P	N/P	N/P	**4336**	**10,143**	**7443**	**13,505**	**11,072**
Low/absent NK cell activity	Failed	N/P	N/P	N/P	N/P	**Low**	Nl	N/P	Nl	Nl
HLH criteria[b]	6/7	5/7	5/6	5/6	5/5	7/8	6/7	5/6	5/7	5/7

Parameters fulfilling the HLH diagnostic criteria are indicated in **bold**. Abbreviations: F, female; M, male, Y, yes; N, no; N/A, not available; N/P, not performed; ANC, absolute neutrophil count; NK, natural killer; Nl, normal.

[a] CNS involvement with *Ehrlichia*.

[b] This row represents the number of abnormal criteria relative to the number of tested criteria.

Table 6
Patients' laboratory data at initial presentation comparing HLH versus non HLH patients (values are presented as medians with ranges in parentheses).

Blood test	HLH patients (N = 25)	Non HLH patients (N = 132)	p-Value
WBC count ($\times 10^3$/μL)	2.2 (0.4–15.5)	3.1 (0.8–39)	0.63
Hemoglobin (g/dL)	8.8 (7.5–14.3)	10.9 (6.1–17.3)	0.016
Platelets ($\times 10^3$/μL)	38 (15–84)	64 (3–454)	0.003
Ferritin (μg/L)	13,764 (1766–85,517)	2869 (165–53,423)	< 0.001
Serum creatinine (mg/dL)	1.59 (0.7–8.17)	1.09 (0.3–6.2)	0.023
BUN (mg/dL)	25 (7–85)	17 (3–83)	NS
PT (s)	14.7 (9.8–24.5)	15 (9.7–103)	NS
PTT (s)	35.9 (4.6–187.8)	40.8 (24.3–86.7)	NS
Fibrinogen	178 (71–379)	214 (25–578)	NS
Serum protein (g/dL)	5.6 (4.4–6.7)	5.7 (4.2–7.9)	NS
Serum albumin (g/dL)	3 (2.1–3.9)	3.1 (2.0–4.8)	NS
Alkaline phosphatase (IU/L)	113 (43–493)	103 (24–586)	NS
AST (IU/L)	155 (43–3680)	116 (16–1855)	0.009
ALT (IU/L)	120 (29–1269)	93 (16–1264)	NS
LDH (IU/L)	849 (327–6860)	512.5 (149–3100)	< 0.001

Abbreviations: WBC: white blood cell; BUN: blood urea nitrogen; PT: prothrombin time; PTT: partial thromboplastin time; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; NS: not significant.

treatment is initiated early before confirmatory testing especially when there is a history of tick bites in an endemic area during increased tick activity seasons. It should be noted that a negative history of tick bite does not rule out the possibility of ehrlichiosis. The treatment of choice is doxycycline [17].

Transplant patients who receive chronic immunosuppressive therapy are at risk of acquired infections, including *Ehrlichia.* It can be challenging for physicians to consider ehrlichiosis in transplant patients as many of the presenting clinical and laboratory findings of ehrlichiosis including cytopenias and elevated liver enzymes can be attributed to immunosuppressive medications. Previous studies have reported the clinical characteristics and outcomes of transplant patients with ehrlichiosis [7–9,18,19]. Thomas and colleagues reported on 15 transplant recipients with ehrlichiosis, and found a trend toward more *E. ewingii* infections in transplant patients when compared to immunocompetent patients (p = .08) [7]. Our results concurred with these findings with *E. ewingii* infections being significantly more prevalent among transplant recipients (4.5% vs. 1.9%; p = .035; Table 2). Our results showed that transplant patients had more leukopenia and renal dysfunction than immunocompetent patients, which compared well with the findings by Thomas et al. Although leukopenia could be due to the infection, it might have been more pronounced in transplant recipients due myelosuppressive medications. Contrary to Thomas's study, our transplant patients did not have lower hepatic enzymes compared to non-transplant patients.

In a larger series, Lawrence and colleagues described the clinical outcome of 25 transplant recipients with ehrlichiosis [9]. Although this study was conducted at the same institution where we conducted our study, Lawrence and colleagues' study was done during the period of January 1996 through December 2007 while our study spanned the period May 2007 through October 2016, with only 8-month overlap. Our study showed that the outcome of *Ehrlichia* infection was comparable between transplant and non-transplant patients; results that are shared with those from Thomas et al. [7]. The length of hospital stay was comparable between the two groups and only 2 immunocompetent patients died during admission from end organ failure and septic shock.

Although *Ehrlichia*-induced HLH has been reported in the literature [11,20–28], there are no studies evaluating the occurrence rate of HLH among patients with ehrlichiosis. *Ehrlichia* can induce excessive cytokine production which is believed to contribute to the septic shock-like clinical presentation seen in some HME cases [29]. *Ehrlichia* can trigger a hyper inflammatory response, thus making HLH on the differential diagnosis of patients presenting with a history of tick bites and clinical and laboratory findings suggestive of HLH. In the current study which reported on the largest series of ehrlichiosis, we estimated the occurrence rate of *Ehrlichia*-induced HLH. We used the H-Score calculator to determine the likelihood of HLH as many of the patients were not considered for that diagnosis and did not have all HLH-2004 diagnostic criteria tested or available. The H-Score has been validated for the diagnosis of secondary HLH in adults [13] and was tested with good performance in adults and pediatric patients [30]. The occurrence rate of *Ehrlichia*-induced HLH was at least 16%. Although HLH often has a dismal prognosis with an overall mortality of up to 75% [20,31,32], the prognosis of *Ehrlichia*-induced HLH is more favorable. Our results are in line with this observation as we only had one mortality among the 25 *Ehrlichia*-induced HLH patients. However, *Ehrlichia*-induced HLH patients had longer hospital stay and more abnormal laboratory findings (anemia, thrombocytopenia, renal failure) which are suggestive of more severe disease.

Our study has limitations. This is a retrospective study that was dependent on data collected from medical charts and hospital records. Only information that was documented could be used in our analysis; thus we cannot exclude the possibility of undocumented information or inaccurate diagnoses. A potential bias could be that transplant patients may have been more likely to seek medical attention and have closer followup in the setting of febrile illnesses as compared to non-transplant patients. In addition, the occurrence rate of *Ehrlichia*-induced HLH could be an under estimation of the true occurrence rate even with the use of H-Score. The H-Score might not be optimized to accurately calculate HLH probability as it does not include some of the very common abnormalities seen in HLH patients such as renal failure, hypoalbuminemia, and coagulation system alterations.

In conclusion, we have reported our experience with *Ehrlichia* infections; we believe our investigation included the largest series of cases reported to date in the medical literature comparing the clinical outcomes between transplant and non-transplant patients. Ehrlichiosis should be considered by physicians as a possible diagnosis for patients who develop fever and laboratory findings suggestive of the infection especially in patients with seasonal tick exposure or who reside in endemic areas. The diagnosis might be challenging in transplant patients who present with similar findings that can be attributed to immunosuppressive medications or graft versus host disease. A high index of suspicion should be maintained and empiric antibiotics should be initiated. *Ehrlichia*-induced HLH is a potential serious complication with relatively high occurrence rate among patients with ehrlichiosis; patients manifest severe disease with end organ damage requiring longer hospital stay. However, patients' outcome seems to be comparable to those without HLH.

Conflicts of interest

Nothing to disclose.

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