Boletín Médico del
Hospital Infantil de México

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CLINICAL CASE

First report of pediatric ehrlichiosis in Mexico

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Abstract

Background: *Ehrlichia chaffeensis is responsible for most cases of human ehrlichiosis, an acute febrile tick-borne disease. This clinical entity is more commonly reported in adults from the United States. Therefore, it is of special interest to characterize this disease in children, given that very few cases in children have been reported outside of this country.* **Case report:** *We describe the case of a 15-year-old female from northeastern Mexico with a five-day history of myalgias, arthralgias, fever, abdominal pain, rash, and somnolence. The possibility of tick-borne disease was suspected considering that she lived with three tick-infested dogs that had recently died and a neighbor with similar symptoms who deteriorated rapidly and died a week earlier. Ehrlichia spp. was detected in blood samples by polymerase chain reaction. The patient completed a seven-day course of doxycycline and was discharged with complete resolution of symptoms.* **Conclusions:** *This case is the first report of ehrlichiosis in a pediatric patient in Mexico, illustrating the importance of considering tick-borne diseases as a differential diagnosis in patients with rash, fever, and altered level of consciousness. This initial clinical presentation may be indistinct from other conditions such as dengue, meningococcemia, and multisystem inflammatory syndrome in children (MIS-C), among others.*

Keywords: *Ehrlichia spp. Ehrlichiosis. Human monocytic ehrlichiosis. Tick-borne disease. Children.*

Primer reporte de ehrlichiosis pediátrica en México

Resumen

Introducción: *Ehrlichia chaffeensis es responsable de la mayoría de los casos de ehrlichiosis humana, una enfermedad febril aguda transmitida por garrapatas. Esta entidad clínica se reporta con mayor frecuencia en adultos de Estados Unidos. Por lo tanto, es de especial interés caracterizarla en niños, dado que se han reportado muy pocos casos en niños fuera de este país.* **Caso clínico:** *Se describe el caso de una paciente de sexo femenino de 15 años, originaria y residente del noreste de México con una historia de cinco días de mialgias, artralgias, fiebre, dolor abdominal, erupción cutánea y somnolencia. Se sospechó la posibilidad de una enfermedad transmitida por garrapatas considerando que convivió con tres perros infestados de garrapatas que habían muerto recientemente y una vecina con síntomas similares, quien se deterioró rápidamente y murió una semana antes. Ehrlichia spp. se detectó en una muestra sérica mediante reacción en cadena de la polimerasa. La paciente completó un curso de siete días de doxiciclina y fue dada de alta con resolución de los síntomas.* **Conclusiones:** *Este caso es el primer reporte de ehrlichiosis en un paciente pediátrico en México que ilustra la importan-*

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Date of reception: 02-03-2022
Date of acceptance: 07-06-2022
DOI: 10.24875/BMHIM.22000056

Available online: 12-07-2023
Bol Med Hosp Infant Mex. 2023;80(Supl 1):12-22
www.bmhim.com

cia de considerar enfermedades transmitidas por garrapatas dentro del diagnóstico diferencial de pacientes con exantema, fiebre y alteración del estado de conciencia. Esta presentación clínica inicial puede ser indistinguible de otras entidades como dengue, meningococcemia y síndrome multisistémico inflamatorio, entre otras.

Palabras clave: *Ehrlichia spp. Ehrlichiosis. Ehrlichiosis monocítica humana. Enfermedad transmitida por garrapatas. Niños.*

Introduction

Human ehrlichiosis is an acute febrile tick-borne disease considered a zoonotic infection, caused by bacteria of the *Ehrlichia* genus, being *Ehrlichia chaffeensis* the most common cause[1-4]. Most cases are reported in adults from the eastern and southcentral regions of the United States of America (USA), and 49% require hospitalization[5,6]. Death occurs in 1-2% of untreated infections, and symptoms may be indistinguishable from other conditions, such as other vector-borne diseases, meningoencephalitis, or the recently described multisystem inflammatory syndrome in children (MIS-C); thus, diagnostic suspicion is needed to initiate antimicrobial therapy, especially when tick bite history is lacking[7-9].

Only twenty-three cases of human ehrlichiosis in children and adolescents outside of the USA have been reported to date[4,7,10-15]. We present the first pediatric case of ehrlichiosis in Mexico and the fourth in Latin America. We also performed a literature review of *Ehrlichia* spp infection affecting children to identify demographics, clinical characteristics, and outcomes.

Clinical case

We present the case of a previously healthy 15-year-old female from an urban area in northeastern Mexico presented to the emergency department with a five-day history of persistent fever, chills, malaise, headache, myalgias, arthralgias, vomiting, and generalized rash. Four days earlier, her neighbor had been admitted to our hospital with septic shock and disseminated intravascular coagulation (DIC) and died within 8 hours of admission with no infectious agent identified. On directed questioning, the parents admitted having three tick-infested dogs that had died the previous week. Upon admission, vital signs evidenced a fever of 38.8°C, tachycardia, tachypnea, and hypotension. In addition to an altered level of consciousness, her physical examination revealed meningeal signs, along with a maculopapular rash that involved palms and soles, and a skin lesion of 1 cm in diameter, with a necrotic central area and surrounding erythema in her left ankle (Figure 1). A clinical syndrome of meningoencephalitis was diagnosed. In addition, the possibility of a tick-borne infection was raised by considering the history of tick-infested dogs and the epidemiological link to the deceased neighbor.

Laboratory results demonstrated anemia and thrombocytopenia in the complete blood count: hemoglobin 9.6 g/dL (normal range: 12-14 g/dL); white blood cells 6,200/mm^3 (normal range: 4,000-11,000/mm^3); neutrophils 4,650/mm^3 (normal range: 2,000-7,500/mm^3) (75%); lymphocytes 1,240/mm^3 (normal range: 1,000-4,800/mm^3) (20%); platelets 116,000/mm^3 (normal range: 150,000-450,000/mm^3). Also, mildly elevated serum hepatic transaminase values were detected: alanine aminotransferase 71 UI/L (normal range: 4-36 UI/L); aspartate aminotransferase 77 UI/L (normal range: 8-33 UI/L); elevated acute phase reactants: C-reactive protein 90 mg/L (normal range: <10 mg/L); erythrocyte sedimentation rate 25 mm/h (normal range: 0-20 mm/h); hyperfibrinogenemia 650 mg/dL (normal range: 200-400 mg/dL), and elevated lactic dehydrogenase 366 UI/L (normal range: 140-280 UI/L); D-dimer 859 ng/ml (normal range: <500 ng/ml) and serum ferritin 223 ng/ml (normal range: 12-150 ng/ml). Nasopharyngeal swabbing for PCR (polymerase chain reaction) detection of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), serum IgM, and IgG serology were negative. Head computed tomography was normal, with no meningeal enhancement reported by the Neuroradiology Department. A lumbar puncture was performed, demonstrating a high opening pressure of 320 mmH_2O (normal range: 70-180 mmH_2O) with a clear cerebrospinal fluid (CSF) appearance. CSF white blood cell count 402/mm^3 (normal range: < 5 cell/mm^3); 90% polymorphonuclears; pH: 8.5; glucose 59 mg/dL (normal range: 45-80 mg/dL); proteins 107 mg/dL (normal range: 15-45 mg/dL); chloride 122 mmol/L (normal range: 120-130 mmol/L); some crenated erythrocytes; lactate 2.4 mmol/L (normal range: 1.5-1.9 mmol/L), and no microorganisms were observed on Gram stain. CSF and blood cultures were also sent. Electroencephalogram (EEG) showed bilateral and diffuse cortical and subcortical moderate dysfunction with no epileptic activity.

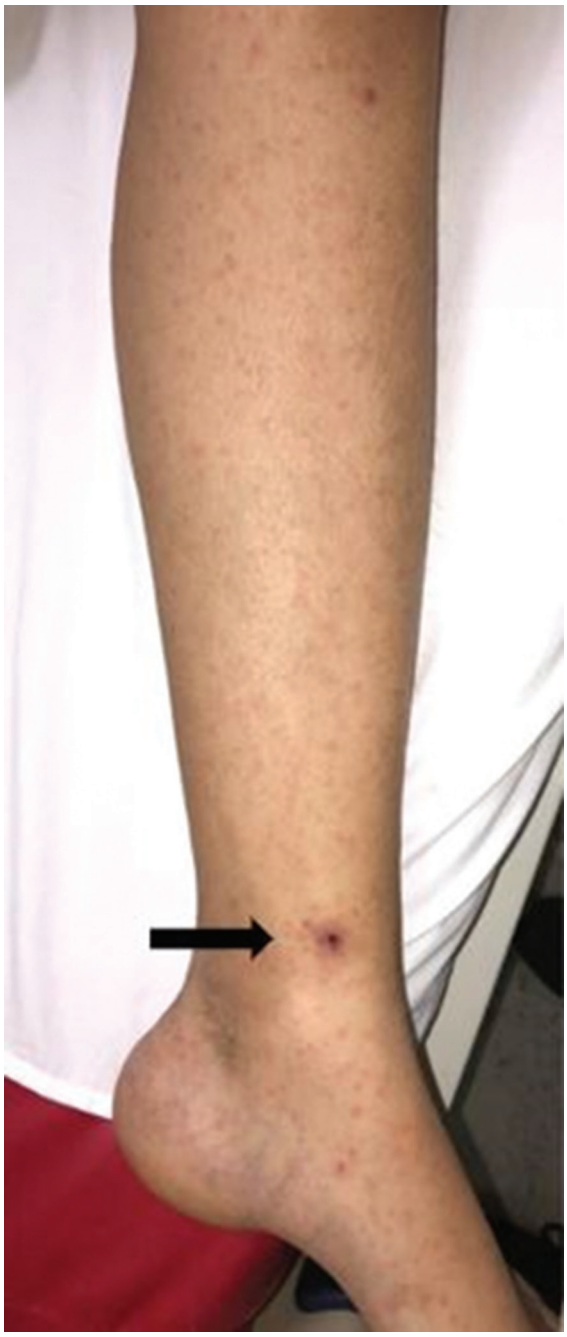

Figure 1. Maculopapular rash in a patient with ehrlichiosis. Black arrow: 1 cm erythematous macule with a necrotic central area corresponding with tick-bite.

CSF PCR FilmArray Meningitis/Encephalitis Panel (BioFire®) and serologic titer tests for tick-borne diseases were requested, but they were not processed due to in-house laboratory unavailability of reagents. A serum sample for detecting some tick-borne diseases by PCR was sent to the Center for Research and Development in Health Sciences (CIDICS) of the Universidad Autónoma de Nuevo Léon. This test included molecular detection of *Rickettsia* spp, *Babesia* spp, *Anaplasma* spp, and *Ehrlichia* spp. Empirical therapy for meningoencephalitis was initiated with intravenous ceftriaxone (100 mg/kg/day) and vancomycin (60 mg/kg/day). Taking into consideration a high suspicion of tick-borne infections, doxycycline (100 mg/twice a day via nasogastric tube) was also included. The patient was admitted to the pediatric intensive care unit, requiring invasive mechanical ventilation and vasopressors for three days. Ceftriaxone and vancomycin were suspended after 72 hours, as CSF and blood cultures did not report any bacterial growth. Doxycycline was continued for seven days as rickettsial disease persisted as the main diagnostic impression. The patient showed subsequent clinical improvement, which allowed her transfer to the General Pediatrics ward on her seventh day of hospital stay. A week after admission, the serum PCR detection of *Ehrlichia* spp. was reported. No adverse or unanticipated events related to treatment or hospitalization occurred, and the patient was discharged after ten days of hospital stay with complete resolution of symptoms.

Discussion

Tick-borne diseases (TBD) are caused by bacteria, viruses, and parasites, including *Anaplasma phagocytophilum*, *Babesia* spp., *Borrelia burgdorferi*, *Ehrlichia* spp., Powassan virus, *Rickettsia* spp., among others[16,17].

Ehrlichiosis is caused by bacteria from *Ehrlichia* genus, including *E. chaffeensis, E. ewingii* and *E. muris subsp. Eauclairensis*[1-4]. *Ehrlichia* spp. are Gram-negative, obligate intracellular bacteria that grow in leukocytes in membrane-bound vacuoles and can infect humans and other vertebrate mammals, such as deer, rodents, dogs, sheep, and goats, and thus considered a zoonotic infection. Furthermore, its clinical presentation has been primarily described in adults[1-4].

E. chaffeensis is the most common cause of human ehrlichiosis. Dawson et al. reported the first case in 1991[1-4,18]. The frequency of ehrlichiosis is rising, probably due to increased clinical recognition and availability of serological and molecular diagnostic tests[19].

Ehrlichiosis is primarily acquired through the bite of an infected tick, although cases of spread through blood transfusion and organ transplant recipients have been reported[3,4,20]. It has been demonstrated that

E. chaffeensis can survive for up to a week in refrigerated blood[3].

Ticks that can spread the bacteria to humans include *Ixodes scapularis* (black-legged tick), found in south-central and eastern USA, transmitting *E. muris subsp. eauclairensis*, and *Amblyomma americanum* (lone star tick), which spreads *E. chaffeensis* and *E. ewingii*, and is distributed in eastern USA[3,20,21].

Ticks become infected after feeding from their primary reservoir host, such as the white-tailed deer (*Odocoileus virginianus)* for the lone star tick[20,22]. Transmission to humans usually occurs during summer months, with a reported peak during June and July, and is most frequently reported in men than women[3,4,23,24].

We performed a literature search of core databases including Medline (US National Library of Medicine [NLM]), SciELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Literature in Health Science), Scopus (Elsevier, Amsterdam, Netherland), the Excerpta Medica Database (Embase [Elsevier, Amsterdam, Netherlands]) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL [EBSCO, Ipswich, Massachussetts]) Other databases included Europe PMC (European Bioinformatics Institute) and Web of Science (Clarivate Analytics, Philadelphia, Pennsylvania) between 1989 and 2021 using a combination of the keywords "*Ehrlichia spp*", "*Ehrlichiosis*", "human monocytic ehrlichiosis" with a narrow search specific to pediatric cases (0-18 years). We included articles published between January 1989 and May 2021, with children and adolescents between 0 and 18 years of age and a confirmed *Ehrlichia* spp. infection. All case reports and case series were included, and references were reviewed to identify additional cases and to detect duplicates.

We identified twenty-three cases of ehrlichiosis in children and adolescents, including the present case[4,5,7,10,12-14,20,25-34]. A summary of the cases of pediatric ehrlichiosis is shown in Table 1.

Similar to what has been previously described in adults, we found a slightly higher predominance of ehrlichiosis in males (male-to-female ratio 1.1:1), and *E. chaffeensis* was the most frequently identified species, corresponding to 47.8% (n = 11)[3,23,35].

Signs and symptoms of ehrlichiosis generally appear within one or two weeks after the bite of an infected tick. It is important to mention that tick bites are typically painless, thus some patients may not notice them[3,4,20-22]. We found that tick exposure or tick bite was only reported in 65.2% (n = 15) of children and adolescents. In this patient, exposure was demonstrated, as the family acknowledged having tick-infested dogs that had recently died. Although the parents did not explicitly refer history of a tick bite, the physical examination demonstrated a skin lesion compatible with a tick bite.

Infection with *Ehrlichia* spp. ranges from asymptomatic to fatal illness[3,4,21]. It has been reported that up to 13% of children in endemic areas may present an asymptomatic infection[21]. In those who present symptoms, early manifestations of the disease include fever, chills, fatigue, headache, myalgia, arthralgia, nausea, vomiting, loss of appetite, diarrhea, cough, and petechial or maculopapular rash involving the trunk, which presents in children in up to 66% of the cases, compared to 36% to 47**%** of infected adults[3,4,15,20-22,30,36]. Although clinical manifestations of ehrlichiosis may be similar in adults and children, some tend to appear more frequently in younger patients, such as neurological involvement and rash[3,15,37].

A retrospective study including 32 children with confirmed or suspected ehrlichiosis in six areas located in the "tick belt" of the Southeastern United States, of which only 14 were confirmed cases, found the following prevalence of symptoms: fever 100%, headache 69%, myalgia 69%, rash 66%, nausea or vomiting 56%, altered mental status 50% and lymphadenopathy 47%[35].

The triad of fever, headache, and petechial or maculopapular rash, associated with rickettsial diseases, was only present in 48% of our cases[29,38]. Although not presented all concomitantly, those three symptoms were the most common. This clinical triad was present in our patient.

Fever was reported in all cases. Rash and headache were present in 60.9% (n = 14) and 52.1% (n = 12), respectively. Altered mental status was present in 52.1% (n = 12) and abdominal pain in 39.1% (n = 9) of cases (Table 2).

Data on symptom duration was available in 19 out of 23 cases, ranging from 1 to 30 days. The median duration of symptoms prior to antimicrobial therapy and hospitalization was seven days, similar to the six to nine days of medians previously reported[19,35].

If antibiotic treatment is delayed, late manifestations of the disease can cause severe illness with various complications, including septic shock, meningoencephalitis, respiratory failure, DIC, organ failure, and death[3,4]. Another complication that has been related to ehrlichiosis is hemophagocytic lymphohistiocytosis (HLH)[20,22]. Some risk factors described for severe illness include antibiotic treatment delay, young or old age, and

Table 1. Published data on risk factors, treatment, and outcomes of human ehrlichiosis in children

Year/ Author/ Country	Age/ Gender	Underlying disease	Clinical features	Evolution time at arrival to ER room	Species and method of diagnosis	Laboratory findings	Tick bite or exposure to infected dogs	Antibiotic treatment and duration	Complications	Outcome
1989 Doran[25] USA	4 / F	None	Fever, headache, lethargy, emesis, malaise	30 days	*E.canis* Serology titers 1:640; 1:20,480	Anemia, leukopenia, lymphopenia, thrombocytopenia, 8% bands, high levels of AST, ALT and LDH	Tick bite in hairline (1 month and 1 week earlier)	Ceftazidime (7 days) Oxacillin (7 days) Chloramphenicol (10 days)	DIC	Alive
1992 Hammill[26] USA	9 / F	None	Fever, headache, malaise, weakness, anorexia, chills, neck pain, myalgias, abdominal pain, confusion	15 days	*Ehrlichia spp* Serology titers 1:64; 1:8,192	Leukopenia, lymphopenia, 65% bands, thrombocytopenia, high levels of AST and ALT	None	Gentamicin (ND) Cefotaxime (ND) Nafcillin (ND) Chloramphenicol (7 days)	DIC	Alive
1992 Rathore[27] USA	3 / M	None	Fever, malaise, petechial rash, emesis, somnolence	1 day	*Ehrlichia spp* Serology titers < 1:16; 1:128	Leukopenia, lymphopenia, high SCr, bandemia, high levels of AST and ALT.	Exposure to ticks (not bite)	Cefotaxime (ND) Chloramphenicol (14 days)	DIC, septic shock, meningoencephalitis	Alive
	2 / F	None	Fever, lymphadenopathy, rash, irritability, splenomegaly	6 days	*E.canis* Serology titers 1:128; 1:4,096	Leukopenia, lymphopenia, 28% bands, thrombocytopenia, high levels of AST, ALT	Exposure to tick bites (3 weeks earlier)	Cefuroxime (ND) Gentamicin (ND) Chloramphenicol (14 days)	None	Alive
1993 Fichtenbaum[28] USA	6 / M	None	Fever, abdominal pain, petechial rash, myalgias, photophobia, lethargy	7 days	*Ehrlichia spp* Serology titers 1:32; 1:512	Leukopenia with bandemia, thrombocytopenia, high levels of AST, ALT	Exposure to tick bites (12 days earlier)	Ceftriaxone (10 days) Chloramphenicol (10 days)	DIC, hypotension, pneumonia, respiratory failure, ECMO PARDS, meningoencephalitis	Dead
	13 / F	None	Fever, chills, rash, conjunctivitis	ND	*Ehrlichia spp* Serology titers 1:2,048; 1:2,048	Leukopenia, thrombocytopenia, high levels of AST, ALT	Exposure to ticks (not bite)	Oxacillin (10 days) Penicillin (10 days) Chloramphenicol (10 days)	DIC, hypotension, septic shock, pulmonary edema	Alive
	7 / F	None	Fever, chills, rash	ND	*Ehrlichia spp*	Leukopenia,	Exposure	Tetracycline	DIC, hypotension,	Alive

(Continues)

Table 1. Published data on risk factors, treatment, and outcomes of human ehrlichiosis in children *(continued)*

Year/ Author/ Country	Age/ Gender	Underlying disease	Clinical features	Evolution time at arrival to ER room	Species and method of diagnosis	Laboratory findings	Tick bite or exposure to infected dogs	Antibiotic treatment and duration	Complications	Outcome
					Serology titers < 1:64; 1:512	thrombocytopenia, high levels of AST, ALT	to ticks (not bite)	(7 days)	encephalitis	
1996 Arraga[12] Venezuela	1 / F	None	Fever, rash, hepatosplenomegaly, generalized seizures	21 days	*E.chaffeensis* 1:16; 1:128	Anemia, leukopenia, thrombocytopenia, high levels of AST, ALT	None	Tetracycline (10)	DIC, pneumonia, meningoencephalitis, PICU stay, septic shock, acute respiratory failure. Relapse eight months after discharge	Alive
1999 Buller[29] USA	11 / M	Kidney transplant	Fever, headache, nasal congestion, myalgias, stiff neck, lymphadenopathy	ND	*E. ewingii* PCR Serology titers ND; 1:2,048	Anemia, thrombocytopenia	Tick exposure (1 month earlier)	Vancomycin (ND) Ceftazidime (ND) Doxycycline (10 days)	None	Alive
2000 Peters[30] USA	16 / M	None	Fever, headache, myalgias, migratory arthralgias, fatigue, petechial rash, chest pain, rigors, conjunctivitis	30 days	*E.chaffeensis* PCR	Hyponatremia, leukopenia with bandemia (20%), thrombocytopenia, high levels of AST, ALT	Exposure to tick bite (1 month earlier)	Ceftriaxone (ND) Vancomycin (ND) Doxycycline (14 days)	DIC, respiratory failure, pneumonia, PICU stay	Alive
2005 Louw[13] South Africa	6 / M	None	Fever, headache, ataxia, lethargy, somnolence	days	*E. ruminantium* PCR	Leukocytosis, thrombocytosis	ND	ND	Meningoencephalitis, PICU stay	Dead
2008 Martínez[7] Venezuela	9 / M	None	Fever, anorexia, headache, abdominal pain, conjunctivitis, hepatomegaly, rash, somnolence	3 days	*E.chaffeensis* PCR	Thrombocytopenia	Exposure to tick bites (6 weeks earlier)	Doxycycline (14 days) Chloramphenicol 8 days)	None	Alive
2010 Burns[31]	10 / M	None	Fever, altered mental status, generalized	5 days	*E. chaffeensis* PCR	Pancytopenia, hypofibrinogenemia	ND	Doxycycline (10 days)	DIC, hypotension, meningoencephalitis	Alive

(Continues)

Table 1. Published data on risk factors, treatment, and outcomes of human ehrlichiosis in children *(continued)*

Year/ Author/ Country	Age/ Gender	Underlying disease	Clinical features	Evolution time at arrival to ER room	Species and method of diagnosis	Laboratory findings	Tick bite or exposure to infected dogs	Antibiotic treatment and duration	Complications	Outcome
USA			seizures, lethargy, hepatosplenomegaly			hypertriglyceridemia, elevated serum ferritin			HLH	
2011 Hanson[32] USA	10 / F	None	Fever, rash, headache, fatigue, photophobia, irritability, abdominal pain, cough	8 days	*E. chaffeensis* Serology titers IgM 1:80; 1:320 IgG 1:258; 1: 1,024	Leukopenia, thrombocytopenia, elevated serum ferritin	ND	Cefepime (ND) Doxycycline (ND)	HLH, hypotension, PICU stay	Alive
	13 / M	None	Fever, headache, fatigue, hyporexia, rash, lymphadenopathy, generalized seizures	7 days	*E. chaffeensis* PCR Serology titers ND	Anemia, leukopenia, thrombocytopenia, high levels of LDH, uric acid and elevated serum ferritin	Exposure to tick bites	Vancomycin (ND) Gentamicin (ND) Clindamycin (ND) Doxycycline (ND)	HLH, hypotension, respiratory failure, PICU stay	Alive
2013 Antoon[33] USA	4 / M	None	Fever, headache, abdominal pain, hyporexia, night sweats, weight loss, hepatosplenomegaly	30 days	*E. chaffeensis* PCR	Leukocytosis, anemia, thrombocytopenia, high levels of ALT, AST, GGT, LDH, hyponatremia, hypoalbuminemia	None	Ceftriaxone (2 days) Vancomycin (2 days) Doxycycline (21 days)	Meningitis, pleural effusion, ascites	Alive
2015[5] Otrock USA	16 / F	None	Fever	ND	*E. chaffeensis* PCR	Anemia, neutropenia, thrombocytopenia, elevated serum ferritin	ND	Doxycycline (ND)	HLH	Alive
2015[34] Statler USA	7 / F	None	Fever, abdominal pain, rash, irritability	6 days	*E. chaffeensis* PCR	Pancytopenia, high levels of AST and ALT	ND	Doxycycline (ND)	HLH, ARDS	Alive
2015 Vijayan[10] USA	7 / M	None	Fever, rash, abdominal pain, conjunctivitis, hepatosplenomegaly	12 days	*E. chaffeensis* Serology titers IgM 1:2,048; 1:8,192 IgG 1:4,096; 1:16,384	Anemia, leukopenia, lymphopenia, thrombocytopenia, high levels of AST and ALT, hypoalbuminemia	Exposure to tick bites	Ceftriaxone (ND) Vancomycin (ND) Doxycycline (7 days)	HLH, hypotension, pleural effusion, ascites, PICU stay	Alive

(Continues)

Table 1. Published data on risk factors, treatment, and outcomes of human ehrlichiosis in children *(continued)*

Year/ Author/ Country	Age/ Gender	Underlying disease	Clinical features	Evolution time at arrival to ER room	Species and method of diagnosis	Laboratory findings	Tick bite or exposure to infected dogs	Antibiotic treatment and duration	Complications	Outcome
2016 Cheng[20]	9 / M	None	Fever, chills, hepatosplenomegaly	4 days	*E. chaffeensis* PCR	Anemia, leukopenia, thrombocytopenia, high	Tick exposure	Vancomycin (ND) Ceftriaxone (ND)	HLH DIC	Alive
USA			lethargic			levels of AST and ALT		Doxycycline (ND)	ALF AKI ECMO (140 hours)	
2019 Emiroğlu[4] Turkey	6 / M	None	Fever, chills, headache, anorexia, conjunctivitis	10 days	*Ehrlichia spp* PCR	Lymphopenia, hyponatremia	Tick exposure	Doxycycline (10 days)	None	Alive
2021 De la Espriella[14] Colombia	12 / F	None	Fever, rash, headache, abdominal pain and conjunctivitis	9 days	*Ehrlichia spp* PCR	Leukopenia, neutropenia, lymphopenia, thrombocytopenia, hyponatremia, high levels of AST and ALT	Tick exposure	Doxycycline (14 days) Ceftriaxone (7 days)	Meningitis	Alive
Present case México	15 / F	None	Fever, rash, myalgias, abdominal pain, headache, somnolence	6 days	*Ehrlichia spp* PCR	Anemia, thrombocytopenia, high levels of AST and ALT	Tick bite	Vancomycin (7) Ceftriaxone (7) Doxycycline (7)	Meningoencephalitis, PICU stay	Alive

Serology titers shown as acute phase titer; convalescent phase titer.
AKI: acute kidney injury; ALF: acute liver failure; ALT: alanine aminotransferase; ARDS: acute respiratory distress síndrome; AST: aspartate aminotransferase; DIC: disseminated intravascular coagulation; ECMO: extracorporeal membrane oxygenation; F: female; GGT: gamma-glutamyl transferase; HLH: hemophagocytic lymphohistiocytosis; LDH: lactate dehydrogenase; M: male; ND: no data; PCR: polymerase chain reaction; PICU: Pediatric Intensive Care Unit; SCr: serum creatinine.

Table 2. Clinical signs and symptoms of pediatric human ehrlichiosis

Symptoms	n (%)
Fever	23 (100%)
Rash	14 (60.8%)
Headache	12 (52.1%)
Altered mental status*	12 (52.1%)
Abdominal pain	9 (39.1%)
Conjunctivitis	6 (26%)
Myalgias	5 (21.7%)

*Defined as: irritability, confusion, lethargy, somnolence.

immunocompromise, such as leukemia, solid organ transplants, and human immune deficiency virus[3,20,21,24].

Of 23 cases, only one had risk factors for severe disease, with a history of immunosuppressive therapy with prednisone and azathioprine secondary to a solid organ transplant; however, this patient had a favorable outcome and did not develop life-threatening complications[29].

Severe ehrlichiosis, defined as an illness with complications, was present in 82.6% (n = 19). Complications were reported as follows: DIC (n = 10, 43.4%), HLH (n = 7, 30.4%), meningoencephalitis (n = 9, 39.1%), hypotension (n = 7, 30.4%), respiratory failure (n = 4, 17.3%), septic shock (n = 3, 13%), and need of extracorporeal membrane oxygenation (n = 2, 8.59%).

Laboratory findings in ehrlichiosis include leukopenia, thrombocytopenia, anemia, and elevated transaminases. These last three laboratory alterations were observed in this case report. Other less common findings include hyponatremia and hypoalbuminemia[21]. According to Schutze et al. in their review of confirmed and suspected cases of ehrlichiosis, the most common were thrombocytopenia (94%), elevated aspartate aminotransferase (90%), elevated alanine aminotransferase (74%), hypoalbuminemia (65%), lymphopenia (57%), leukopenia (56%) and hyponatremia (55%)[35]. Common findings in our review were thrombocytopenia (95.6%), elevated aspartate aminotransferase and elevated alanine aminotransferase (65.2%), lymphopenia (26%), leukopenia (69.5%). We found incomplete data on laboratory values concerning sodium and albumin. Hyponatremia and hypoalbuminemia were reported in 13% and 8.6% of the cases, respectively. Although elevated band count is not reported in the literature as part of the laboratory findings, it was remarkable that six patients (26%) had high counts of immature neutrophils[25-28,30].

Diagnosis of ehrlichiosis remains challenging, partly because the clinical presentation may not be easily differentiated from other febrile diseases of higher prevalence in certain areas. Also, because serological and molecular confirmatory tests may be expensive and not extensively available. Differential diagnoses include influenza-like illnesses, other vector-borne diseases (dengue fever, rickettsiosis, babesiosis, malaria), meningoencephalitis, including meningococcal infection, and the recently described multisystemic inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 virus infection[8,38,39]. Given the non-specific clinical presentation, a proper assessment is necessary, including laboratory tests to support the clinician in the diagnosis, considering the possible etiologies based on the epidemiological context and the patient's personal history.

Among confirmatory tests, we found DNA via PCR, isolation of *E. chaffeensis* from a clinical specimen in cell culture, *Ehrlichia* antigen in a biopsy, and an increase in titers of 4-fold or higher between acute and convalescent serum using indirect immunofluorescence antibody assay specific for IgG against *Ehrlichia* antigen[24,40].

Although not readily available at many centers, other methods to confirm ehrlichiosis include the detection of DNA by PCR on a clinical specimen, detection of *Ehrlichia* antigen by immunohistochemical methods in a biopsy or autopsy, or isolation in a cell culture from a clinical specimen. PCR on whole blood during acute illness is an effective and efficient method to confirm ehrlichiosis, as it provides evidence of infection with *Ehrlichia* spp, and can differentiate between species[24]. These molecular techniques were implemented in dogs and humans in the 90s; previously, the diagnosis was mostly made by serological methods[41]. In this literature review, we included cases dating back to 1989. From 1999 to date, we found 13 patients diagnosed by PCR detection (n =13, 56.50%).

The availability of molecular tests to detect *Ehrlichia* spp was pivotal to diagnosing this case as a tick-borne infection, even though the results were not available rapidly. Another limitation to assess this case was the unavailability of diagnostic tests such as the PCR FilmArray Meningitis/Encephalitis Panel (BioFire®) since it includes 14 of the most frequent pathogens that cause meningoencephalitis. Also, the lack of a confirmatory serological test for ehrlichiosis that could

evidence specific antibody increase from acute and convalescent serum.

Doxycycline is the treatment of choice for adults and children and should be continued at least 3 days after the last documented febrile episode[24,37]. The recommended dosage in children is 4 mg/kg per day, every 12 hours[4]. It is well tolerated by children as a 10-day course, and there is no evidence of tooth discoloration with such regimes[21,24]. Considering that antimicrobial delay is associated with severe disease and adverse outcomes, antibiotic therapy should be initiated immediately if the diagnosis is suspected, regardless of pending laboratory work-up or results[3,4,21,24,37]. In this case, the initial clinical presentation, the epidemiological link, and the history of tick exposure were important to suspect a TBD and initiate empirical therapy. Early initiation of doxycycline was pivotal for the survival of our patient.

If appropriate antimicrobial coverage has been established but the fever persists for 48 to 72 hours, another diagnosis or complication, such as HLH, should be considered[4,5,10,20,31,32,34]. In the reviewed cases, persistent fever despite antimicrobial therapy was reported in patients with HLH (30.8%, n = 7).

The reported fatality rate is 1% to 3%, being the highest among the elderly, children, and immunocompromised[4,20,22]. In our review, death occurred in two previously healthy children, corresponding to 8.6% of the cases.

The greatest preventive measure for ehrlichiosis is avoiding exposure to tick bites. The recommendation is to perform tick checks regularly in humans and pets, particularly after returning from tick-infested areas. Another measure is wearing full-coverage clothing, preferably treated with permethrin and repellents containing *n,n*-diethyl-*m*-toluamide (DEET)[17,24].

Although the presence of antibodies against TBD has already been reported in personnel working in veterinary clinics[42], in Mexico, only four cases of human ehrlichiosis in adults have been reported[1,2,43,44]. The first case was reported in 1996 in a 41-year-old male from southern Mexico[2]. In 2013, two female cases were reported, one of them with a fatal outcome (a 31-year-old female from central Mexico)[1,43]. Recently, in 2020, another male case from Mexico City was documented[44]. No additional reports of ehrlichiosis in Mexico involving children were found, and neither cases occurring in the country's northern region. This is the first case of pediatric ehrlichiosis in Mexico and the first case in the north of Mexico.

Ehrlichia spp is not a frequent pathogen related to disease in children, partly because of the lack of widespread availability of diagnostic tools. Infection with these bacteria should be considered in those patients with a fever with known or possible exposure to ticks, especially in endemic areas, since the prevalence in dogs has been estimated at up to 44%[45]. Given that the clinical presentation could be indistinguishable from other diseases caused by arboviruses, other TBDs, meningoencephalitis, and MIS-C, ehrlichiosis should also be considered as a differential diagnosis in patients with a fever, rash, and altered mental status, even with no history of a tick bite. If the diagnosis of ehrlichiosis is suspected, antimicrobial therapy with doxycycline should be initiated readily to avoid progression to severe illness and life-threatening complications.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

No funding.

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