Human monocytic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis*, an obligate intracellular bacterium that infects mononuclear phagocytic cells. We report a unique case of HME diagnosed in a woman who presented with abdominal pain and acute appendicitis during early pregnancy and whose condition progressively deteriorated to adult respiratory distress syndrome.

Human monocytic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis*, an obligate intracellular bacterium that infects monocytes, mononuclear phagocytic cells, and macrophages, including Kupffer cells, splenic macrophages, and macrophages in perivascular infiltrates. The clinical signs and symptoms of HME most frequently include fever, malaise, headache, myalgia, and rigors. As the disease progresses, anorexia, nausea, vomiting, abdominal pain, diarrhea, and rash develop in 30%–60% of patients. Infection also often results in laboratory findings of leukopenia, thrombocytopenia, and increased liver transaminase levels [1, 2].

Although the majority of patients with HME recover without experiencing complications after receiving doxycycline therapy, severe and fatal infections associated with delays in diagnosis and therapy have been reported [1]. Particularly fulminant disease has been observed in immunocompromised patients; severe complications of such disease include meningoencephalitis, adult respiratory distress syndrome (ARDS), and a toxic shock–like syndrome that results in multiorgan failure [1, 3–6]. Delays that lead to a severe outcome occur because of a lack of clinical awareness regarding the ehrlichioses and because their clinical presentation is nonspecific and often suggests localized abdominal organ disease. Despite many case reports of HME in adults and children, the outcome of severe infection in women with HME during pregnancy has not been previously reported. We report a case of HME that was diagnosed during the early pregnancy of a woman who presented with abdominal pain and acute appendicitis and whose condition progressively deteriorated to ARDS.

**Case report.** In the summer of 1999, a 30-year-old woman who was 13 weeks pregnant presented to the emergency department (ED) of a community hospital in a suburban area of Maryland near Washington, DC. She had a 5-day history of spiking fevers (temperature, 39.4°C–40.0°C). In addition, she reported having myalgias, right lower quadrant pain, and 2 episodes of diarrhea. A complete blood cell count and findings of serum chemical analysis and abdominal ultrasound were normal. The patient was given a diagnosis of viral syndrome and was discharged to her home. Four days after discharge from the hospital, the patient returned to the ED with continued fever and lethargy. She was admitted for further evaluation of an acute abdomen.

The patient was a special education teacher who, except for her current symptoms, was healthy. She was married and had a 13-month-old daughter. There were no significant family illnesses. Approximately 2 weeks before the onset of her symptoms, she had visited the Outer Banks of North Carolina.

At the time of admission to the hospital, the patient had a WBC count of 1800 cells/mm³ (normal range, 3800–10,800 cells/mm³), with a differential count that included 26% neutrophils, 61% bands, and 11% lymphocytes. Her platelet count was 90,000 platelets/mm³ (normal range, 130,000–400,000 platelets/mm³), and her hemoglobin level was 11.7 g/dL (normal range, 12–15.6 g/dL). In addition, the patient had evidence of hepatic injury reflected by a serum alkaline phosphatase level of 271 U/L (normal range, 20–125 U/L), an aspartate aminotransferase level of 720 U/L (normal range, 0–42 U/L), and an alanine aminotransferase level of 664 U/L (normal range, 0–48 U/L). Treatment with ceftriaxone, 1 g iv every 24 h, was begun empirically. One day later, she complained of increasing right lower quadrant pain and was scheduled for an emergency appendectomy. During surgery, the patient was found to have a minimally inflamed appendix. Other intra-abdominal and pelvic organs appeared to be normal. One hour after surgery, the
The patient had respiratory decompensation that required intubation and mechanical ventilation. A chest radiograph showed bilateral opaque lung fields, a finding consistent with ARDS. An echocardiogram revealed normal left ventricular function and no valvular disease. An abdominal ultrasound showed right-sided pleural effusions, mild hepatomegaly, and sludge within the gallbladder.

Although the patient did not recall having recently been exposed to ticks, a diagnosis of HME was considered because of findings of leukopenia, thrombocytopenia, and continued fever, and because of the patient’s history of recent travel to a tick-infested region. The patient began receiving therapy with doxycycline, 100 mg iv q12h.

During the next 5 days after therapy, the patient became afebrile, experienced improvement in her respiratory status, and underwent extubation. The abdominal pain resolved. Eight days after therapy, her WBC count was 8400 cells/mm³, and her platelet count increased to 227,000 platelets/mm³. Doxycycline therapy was discontinued. Follow-up serologic tests were negative for Epstein-Barr virus, cytomegalovirus, hepatitis B virus surface antigen, hepatitis B virus surface antibody, hepatitis C virus total antibody, and hepatitis virus A antibody. The titer of IgG antibodies to E. chaffeensis, as determined by immunofluorescent assay (IFA), was 64, and ELISA was negative for the presence of Borrelia burgdorferi antibodies in blood samples obtained during the acute phase of illness. A second E. chaffeensis IgG antibody titer, determined 1 month after determination of the first titer, was 1024; results of serologic tests for the detection of B. burgdorferi antibodies remained negative. Serologic testing for antibodies to Anaplasma phagocytophilum (human granulocytic ehrlichiosis [HGE]) was also performed; the results were negative. The patient was referred back to her primary care physician, who, along with the patient’s pediatrician, reported no long-term sequelae in either the mother or the infant after 1 year of follow-up.

**Materials and methods.** Immediately after surgical resection, the specimen from the appendix was fixed in 10% neutral formalin. Histologic evaluation of the specimen was done by staining some of the sections with hematoxylin-eosin. Because of the abundance of histiocytic cells, PCR was used to test for the presence of Whipple bacillus DNA. Immunohistochemical staining of formalin-fixed, paraffin-embedded tissue was performed retrospectively by use of anti–E. chaffeensis monoclonal antibodies [7].

**Results.** Histologic sections of the appendix demonstrated numerous histiocytes and occasional crypt abscesses (figure 1A and 1B). PCR analyses of the specimen were negative for Whipple disease bacillus infection. Immunohistochemical staining using monoclonal antibodies revealed E. chaffeensis morulae within macrophages in perivascular infiltrates in the appendiceal wall (figure 2A and 2B).

**Discussion.** Although reports of human ehrlichiosis during pregnancy are rare, the veterinary literature contains many references to ehrlichiosis and pregnancy. Neorickettsia (Ehrlichia) risticii, the causative agent of monocytic ehrlichiosis in horses, has been associated with a syndrome called “equine ehrlichial abortion.” In a study by Long et al. [8], 13 pregnant ponies were infected with E. risticii at 90–180 days of gestation. Two infected ponies were euthanized, and 6 ponies aborted at a mean of 217 days of gestation. E. risticii was isolated from 4 of the 5 fetuses recovered. The 5 remaining infected ponies had normal parturition. IFA performed before suckling began resulted in the detection of E. risticii antibodies in 3 of 4 foals delivered at term [8].

Horowitz et al. [9] reported a case of human granulocytic ehrlichiosis (HGE) diagnosed during the postpartum period of a woman who was exposed to ticks 1 week before she delivered a healthy newborn. At 9 days of age, the newborn developed fever and thrombocytopenia, and analysis of peripheral blood smear specimens revealed morulae in 23% of the granulocytes. Although the route of transmission could not be definitely determined, PCR-amplified DNA of A. phagocytophilum both...
in a blood sample obtained from the child and in the *Ehrlichia* species cultured from the mother’s blood sample was identical on restriction fragment-length polymorphism analysis of a region of the 16S–23S rRNA intergenic spacer region. Both mother and child were successfully treated with doxycycline [9].

Doxycycline is the preferred treatment for all forms of ehrlichiosis in humans. However, there is a relative contraindication to the use of tetracyclines and their derivatives during pregnancy because of the potential for development of bony abnormalities and permanent yellow-brown discoloration of the teeth of the fetus, and because of rare cases of acute fatty liver occurring during pregnancy [10]. Despite these risks, the Centers for Disease Control and Prevention (Atlanta, GA) has recommended that doxycycline should be used, albeit with caution, for antimicrobial prophylaxis for pregnant women following exposure to *Bacillus anthracis*, when contraindications are indicated in the use of other appropriate drugs [11]. An alternative therapy was reported by Buitrago et al. [12], who described 2 patients with HGE at 25 and 36 weeks of pregnancy who were treated with rifampin. *E. chaffeensis* also shows in vitro susceptibility to rifampin; however, to date, there are no data on in vivo susceptibility that support the use of rifampin during pregnancy. Although treatment with rifampin may be appropriate for patients with mild disease and can be tried when tetracycline is absolutely contraindicated, further clinical investigations are necessary to evaluate the role of rifampin in the treatment of HME [13, 14].

Although gastrointestinal manifestations occur in up to 60% of patients with HME, the underlying pathophysiologic mechanisms are poorly understood. Pathologic changes in HME include evidence of macrophage activation and hyperplasia in the spleen, bone marrow, lymph node, and liver [1, 4, 5, 7, 15]. Lesions in the intestines include only lymphohistiocytic perivascular infiltrates in submucosa, muscularis, and serosa/adventitia. The findings in this case suggest that infiltration of gastrointestinal structures by infected cells elicits focal lymphohistiocytic inflammation and clinical signs suggestive of a localized process. Similar manifestations are well-recognized complications of Rocky Mountain spotted fever and have led to inappropriate surgical intervention [16, 17]. Such unfortunate circumstances can best be avoided by the correct recognition of the systemic manifestations that accompany rickettsioses and ehrlichioses.

Meningoencephalitis and ARDS have been the most severe complications reported among patients with HME. Anecdotal reports of cases confirm the frequent occurrence of respiratory insufficiency and ARDS, but the mechanisms that underlie this process are poorly understood [3]. Although the frequency of such complications is not known, 7 (11%) of 62 patients with ARDS or severe acute respiratory processes in New York State during 1994–1995 had serologic evidence of infection with an *Ehrlichia* or *Anaplasma* species [18]. Because of the fast progression of and high mortality rate associated with ARDS, these findings lend further support to the idea that ehrlichial infection should be considered in the appropriate clinical situation in patients with ARDS, and treatment with doxycycline should be implemented.

Serologic testing that demonstrates serologic response (serum IgG level, >128) or seroconversion to *E. chaffeensis* antigens in the context of a consistent clinical illness, usually leads to the laboratory diagnosis of infection with *E. chaffeensis* [2, 15]. However, serologic testing during the acute phase of HME can pose diagnostic difficulties because IgG antibodies usually are not detectable during the first 10 days of illness, and because a role for IgM serologic testing has not been established. In addition, the sensitivity and specificity of IFA for the detection of *E. chaffeensis* are not known. Ehrlichial infections may also induce cross-reactive antibody responses, making it important to perform serologic tests for the detection of both *E. chaffeensis* and *A. phagocytophilum*. [15] Thus, alternative laboratory confirmation should be sought [19]. Examination for *E. chaffeensis* morulae in peripheral blood monocytes is insensitive and pro-
vides a presumptive diagnosis only [1]. Other methods for
diagnosis include culture of the organism and PCR analysis of
acute-phase blood samples [16]. Because *E. chaffeensis* was not
considered early in the differential diagnosis of the case reported
here, peripheral smear specimens were not obtained and acute-
phase blood samples were not available for further testing.
When acute-phase or freshly obtained blood samples are no
longer available, immunohistochemical staining of paraffin-
embedded tissue sections by use of anti-*E. chaffeensis* polyclonal
or monoclonal antibodies offers yet another alternative [7].

HME can be a life-threatening and difficult-to-diagnose in-
fec tion. However, early diagnosis and therapy with doxycycline
will most frequently lead to a rapid resolution. The nonspecific
clinical manifestations of HME or a predominance of localized
findings also confounds diagnosis. Infection in pregnancy also
makes it difficult to make therapeutic decisions because tet-
racyclines may be contraindicated.

The case reported here illustrates several concepts that are
critical to an understanding of HME and rickettsial infections
in general. First, the initial presentation of HME may be non-
specific or may inappropriately direct attention toward a single
organ system and away from the recognition of a systemic
process. Second, therapy with doxycycline, even during ad-
vanced disease and pregnancy can be life saving. Until more-

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