Fever with multi-symptom involvement in a migrant worker

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Fever with multi-system involvement in a migrant worker. *Andrea S. Muhar.*

PRESENTATION

A 27-year-old Mexican migrant worker complained of three days of headache, fever, anorexia and nausea without vomiting. He later developed shortness of breath. A friend brought him to the hospital because he had become confused. There were no visual changes, photophobia, stiff neck, myalgias, abdominal pain, diarrhea, sore throat, cough, urinary symptoms, or rash. He had no sick contacts or exposure to animals. He denied insect or tick bites, illicit drug use, or exposure to toxic substances. He had recently visited a spring in a wooded area.

When seen in a local emergency room he was confused and had a fever of 104[degrees] F. Within a short time he had a 30-second tonic/clonic seizure. The hematocrit was 27%, WBC 6,000/[mm.sup.3] with 89% neutrophils, platelet count of 55,000/[mm.sup.3], BUN 40 mg/dl, creatinine 2.5 mg/dl, and potassium 2.5 mEq/L. He was given intravenous fluids with potassium and transferred to the university hospital. Vital signs on arrival were: temperature 97[degrees] F, pulse 100 and regular, respirations 18 and non-labored, blood pressure 120/60 mm Hg. He was in moderate distress complaining of a headache and thirst. The sclerae were injected but not icteric. There was no sinus tenderness. The oral mucosa was dry with dried blood in the oropharynx, but without any lesions. There was no lymphadenopathy. The neck showed mild resistance to flexion and extension but no Brudzinski or Kernig sign. The lungs had crackles at both bases. He had a regular, rapid heart rate without a murmur. The abdomen was tender to palpation in th e right upper quadrant but there was no hepatomegaly. Multiple petechiae were present over the right anterior chest, but no rash. Neurologic examination showed he could follow simple but not complex commands and answered most questions incoherently. Reflexes were symmetrical and he had no Babinski sign.

Liver function tests indicated hepatic involvement and serial cardiac muscle enzymes showed myocardial injury (see "Case Highlights"). Additionally he had thrombocytopenia (platelet count 22,000/[mm.sup.3] and a normal white blood cell count [10,000/[mm.sup.3]] with 30% bands. A chest X-ray film showed pulmonary edema with a small left-sided pleural effusion. The ECG showed sinus tachycardia at a rate of 104 with a nonspecific intraventricular conduction delay. An echocardiogram showed a normal size left ventricle with mild systolic dysfunction and mild global hypokinesis; the ejection fraction was 45-50%; right ventricular systolic function was mildly decreased.

A CT of the head without contrast as well as an MRI were normal. A lumbar puncture showed clear fluid with 160 RECs, 620 WBCs, 3% neutrophils and 97% monocytes, protein 268 mg/dl, and glucose 26 mg/dl. Cryptococcal antigen was negative; herpes simplex virus (HSV) IgG was positive but HSV PCR was negative. Blood, urine, and CSF cultures were sterile. A urine drug screen was negative. Additional tests for HIV, viral hepatitis, cytomegalovirus, mycoplasma, dengue, yellow fever, St. Louis encephalitis, eastern equine encephalitis, leptospirosis, legionella, and Rocky Mountain spotted fever were negative.

A CT of the abdomen and pelvis with contrast showed airspace disease at the lung bases with bilateral effusions, dilation of the duodenum and prominences of small bowel loops but no obstruction; the wall of the right side of the colon was thickened and the liver was mildly enlarged. A liver biopsy showed diffuse micro/macrovescicular steatosis, chronic inflammatory infiltrate with scattered neutrophils in portal and lobular areas, foci of single and confluent hepatocyte necrosis, focal portal and lobular non-caseating granulomas, and features suggestive of lipid vacuoles and fibrin rings suggestive of "doughnut-hole granulomas" suspicious for Q fever.

This man had a febrile illness with multisystem involvement: thrombocyropenia, delirium with aseptic meningitis, myocardial injury, pulmonary edema, and hepatic damage. Extensive tests for an infectious etiology were negative. However, doxycycline was one of many antibiotics given initially because of a suspected rickettsial infection. After seven days of therapy the IFA antibody test for Ehrlichia chaffeensis returned positive (Table 1). He improved rapidly and completed a 14-day course of doxycycline.

DISCUSSION

Ehrlichiosis, a tick-borne infection caused by rickettsia of the genus Ehrlichia, is primarily an animal infection. [1,2,3] With the expansion of human population into wild and rural areas, ehrlichiosis has appeared in man. After a tick bite the organism is phagocytosed by circulating leukocytes and reproduces intracellularly, producing microcolonies called morulae. [3] The morulae rupture and infect other circulating leukocytes. [3]

The first case of human elirlichiosis, an infectious mononucleosis-like illness called Sennetsu fever, was described in 1954 in Japan. [1]

Two species of Ehrlichia cause human ehrlichiosis in the United States, one type infects monocytes and the other type infects granulocytes.[2] Human monocytic ehrlicbiosis (HME) infects mononuclear phagocytes and is caused by Ehrlichia chaffeensis, first isolated in 1986 from the blood of a military recruit with a mild form of the disease on duty at Fort Chaffee, Arkansas. [1,2] Transmission is by the Lone Star tick (Amblyomma americanum), native to the southeastern and south central U.S., the site of HME. [2] The white-tailed deer probably serves as the major reservoir. [2]

About 90% of cases are reported in the South and 75% are men, whose higher level of outdoor activity brings an increased risk of tick exposure. [3] Most cases occur in the late spring and early summer, the season of maximum host-seeking activity by ticks. [1,3]

Human granulocytic ehrlichiosis (HGE) is caused by an organism similar to E. equi which is transmitted by Ixodes species ticks and occurs mostly in the upper Midwest and the northeast region. [1,2] As with HME, most cases occur in the spring and summer. [3]

Clinical features

Although most reported cases of ehrlichiosis describe severe disease, severity is variable. [3] The majority of persons who seroconvert after tick exposure do not have significant illness, [2] but fatalities do occur. Clinical illness typically presents as fever one to two weeks after a tick bite or exposure. Most patients are from rural areas. [3] Table 2 lists common symptoms, signs, and laboratory findings.

Both forms of ehrlichiosis have an undifferentiated presentation with fever, headache, myalgias, fatigue, leukopenia, thrombocytopenia, and elevated aminotransferase levels. Less often, GI, respiratory, and CNS symptoms occur. [1,2] A rash, which occurs more often in children, is noted in a third of patients. It has been described as macular, papular, petechial, or erythematous. [2] The leukocyte count and platelet count are mildly to moderately depressed and aminotransferase levels are typically elevated. [2]

Severe complications include meningoencephalitis (headache, confusion, altered sensorium), adult respiratory distress syndrome, a toxic-shock-like syndrome, renal insufficiency, GI hemorrhage, and fulminant disease in patients immunocompromised by HIV infection or corticosteroid therapy. [1,2]

Diagnosis

Diagnosis is often delayed because of nonspecific symptoms, and most physicians have not seen the disease clinically. [1] Early diagnosis and treatment are associated with a decreased risk of severe complications and death. [2]

The most prominent laboratory finding is leukopenia (usually 1,300 to 4,000 WBC/[mm.sup.3]). Lymphopenia has been found in 80% of cases and neutropenia in 67%. [1] Platelet counts are usually between 50,000 and 140,000/[mm.sup.3], but can be as low as 20,000/[mm.sup.3]. [1,3] Mild anemia occurs in half of cases and the sedimentation rate may be normal or markedly elevated. [3]

Aminotransferases (AST and ALT) may be elevated up to 10 times normal, but bilirubin and alkaline phosphatase are less affected. [3] BUN, and creatinine may be elevated two to three times normal. [3] In HME the CSF may show a moderate lymphocytosis and elevated protein. [3]

Specific diagnostic tests are often not widely available but can be requested from local or state health departments. Diagnosis is made by serologic response (IgG antibody 128 or greater) or seroconversion to E. chaffeensis antigens in the presence of a clinically consistent illness. [2] After an acute serologic test, follow-up in four weeks should show a fourfold or greater rise in titer. [1] But serologic confirmation is usually retrospective, and therefore often not useful in clinical decision-making. [2] Examination of peripheral blood smears for ehrlichia morulae is very insensitive. [2] Polymerase chain reaction (PCR) is a rapid, sensitive, and specific diagnostic method, but not widely available. [2] Cultures take several weeks and are available in only a few research laboratories. [2]

In patients with fever, headache, confusion, leukopenia, thrombocytopenia, myalgias and elevated aminotransferase with a history of tick exposure during warm weather, suspect ehrlichiosis.[1] Differential diagnosis depends on the organ system involved and includes viral illnesses (hepatitis, infectious mononucleosis), meningoencephalitis, leptospirosis, and tick-borne infections such as Rocky Mountain spotted fever or other rickettsioses, babesiosis (protozoan, malaria-like illness), Colorado tick fever (viral) and Lyme disease (spirochetal). [1,3]

Treatment

Treatment should not be delayed pending laboratory confirmation since delay is associated with a worse outcome. [3] The antibiotic of choice is doxycycline, 100 mg twice a day for two weeks. [1] Improvement occurs in 24 to 48 hours. [3] Chloramphenicol can be used but has had in vivo failures; rifampin and the quinolones show in vitro sensitivity but their clinical use has not been determined. [3]

Ehrlichiosis is a relatively newly described disease in the U.S. that many physicians may not be aware of. It should be considered in a patient who presents with headache, fever, and myalgias, especially when accompanied by leukopenia, thrombocytopenia, and aminotransferase elevations. [1] IM

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References

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Ehrlichia chaffeensis antibody

Antibody	Titer	Reference range
IgG	2,048	[less than]64
IgM	320	[less than]20

Symptoms, signs, and laboratory findings in Ehrlichioses

Common findings ([greater than]50% patients)

fever/chills

malaise

headache

myalgias

nausea

leukopenia

thrombocytopenia

[uparrow] aminotransferases

Less common findings

arthralgias

rash

cough

confusion

vomiting

diarrhea

anemia

CSF pleocytosis

CSF [uparrow] protein

[uparrow] BUN and creatinine

Case Highlights

Signs/symptoms:
* Fever, headache, anorexia, confusion, nausea, pulmonary edema, hepatic enlargement

Laboratory results:
* Platelet count: 22,000/[mm.sup.3]
* Liver function tests (reference range)

	albumin (3.5-5.0 g/dl)	2.1 g/dl
	total bilirubin (0.2-1.3 mg/dl)	2.0 mg/dl
	direct bilirubin (0-0.4 mg/dl)	0.7 mg/dl
	alkaline phosphatase (43-122 U/L)	908 U/L
	AST (15-46 U/L)	271 U/L
	ALT (11-66 U/L)	134 U/L
	LDH (313-618 U/L)	5,082 U/L
*	Serial cardiac muscle enzymes (reference range)	
	CK (55-170 U/L)	684, 500, 542 U/L
	CK-MB (0-2.9 ng/ml)	12.6, 8.5, 8.0 ng/ml
	CK-Index (0-2.9)	3.3, 1.7, 1.5
	Troponin I (0-0.03 mcg/L)	0.12 mcg/L

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