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The First Reported Case of Human Monocytic Ehrlichiosis (HME) in Jordan

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Abstract

Human Ehrlichiosis infrequently occurs and can be missed, but attention to history and a meticulous physical examination would raise the index for suspicion and is documented with proper investigations. We report the first case of human monocytic Ehrlichiosis (HME) in a young female patient who lives in the Suburb city of Madaba, Jordan. She presented with fever, severe headache, skin rash, and confusion. She rapidly deteriorated and was admitted to our hospital. She had arrhythmias, convulsions, lapsed into a coma and respiratory failure and needed non-invasive ventilation. In addition to her clinical and epidemiological characteristics, the diagnosis was confirmed by the buffy coat. She had a swift response to oral doxycycline and was discharged home.

Keywords

Ehrlichiosis, Human Monocytic Ehrlichiosis, Buffy Coat

1. Introduction

Ehrlichiosis is a tick-borne disease that is frequently overlooked, though worldwide is showing a progressive increase in the reported cases, the hospitalization rates were observed to be around 50%, and the case-fatality rate was estimated at around 2%. The infection is due to *Ehrlichia chaffeensis*, an obligate intracellular bacterium, and the other similarly named bacteria which later was reclassified as *Anaplasma*. *Ehrlichia chaffeensis* is now synonymous with Human Monocytic Ehrlichiosis (HME), and Anaplasma as Human Granulocytic Ehrlichiosis (HGE) [1].

Ehrlichia was reported to infect other animals like cattle as in a report from

Canada and dogs as in Brazil, as well as sheep and goats. Ehrlichia is a tiny (0.2 - 2 μm) obligate, intracytoplasmic, gram-negative bacteria. Clusters of Ehrlichia multiply in host monocyte vacuoles (phagosomes) to form large, mulberry-shaped aggregates called morulae and are visible in the cytoplasm of infected mononuclear phagocytic cells after 5 - 7 days of infection. Ehrlichiosis is reported more frequently in adults than in children. The highest incidence age range is between 40 and 64 years. Over 90% of patients give a history of tick bites or exposure [2] [3].

The symptoms caused by Ehrlichiosis are nonspecific like fever headaches, malaise, myalgias, rigors, nausea, vomiting anorexia, and confusion [4]. Patients usually have minimal physical examination findings, uncommonly some patients develop mild splenomegaly and hepatomegaly and Lymphadenopathy. Skin rash may not appear and is not considered a common feature of the infection, though infection is more prevalent in adults. Skin rash may appear in up to 60% of children, and fewer than 30% of adults. However, Ehrlichiosis carries an excellent prognosis in healthy hosts. A favorable outcome is associated with the early use of appropriate antibiotics. Here, we report the first diagnosis of human Ehrlichiosis in Jordan, though few were suspected and treated as such without clear diagnostic evidence. This case report increases awareness of the occurrence of such infection in the region.

2. The Case

A 40-year-old female patient, not known to have any chronic medical illness, married, housewife, lives in a village off the city of Madaba, nonsmoker, was admitted through the emergency room on 9 September 2022, she was doing well until 5 days before admission when she started to complain of diffuse headache, gradual onset, progressive, throbbing in nature, not relieved by the over the counter analgesics and associated with generalized fatigue, she sought a neurological consult, a brain CT scan was normal, and she was treated as a case of migraine headache. Three days before her admission to the Specialty Hospital she developed severe arthralgia mostly in her ankles, myalgia, chills, once undocumented fever, nausea, and vomiting. A non-itchy skin rash appeared over her extremities, and there had been no previous similar attack of such symptoms. Her previous history was normal, she was not in direct contact with animals, and she had no recent travel history outside her residence area. She was not on any form of chronic medications except recently one dose for the previously diagnosed migraine at the start of her illness. Her admission examination showed BP 105/67, HR 83/min., RR 20, Temperature 36.6 C, and O_2 sat 98%. She looked ill, and in pain due to her headache and painful ankles, with no focal signs except a red macular rash on her body, mostly on her extremities. While in the hospital her level of consciousness deteriorated, and she had a fever (38.3˚C) on 10 September 2022. An initial septic workup was done, and she was started on parenteral Imipenem/cilastatin 500 mg every eight hours, then she was switched to

piperacillin/tazobactam 4.5 gm every eight hours without a good response. Solumedrol was added the next day without a noticeable response. During her hospital stay, she developed a transient attack of atrial fibrillation with a rapid ventricular response, and she was transferred to the ICU for amiodarone infusion and further observation, and management. In the ICU, she developed nuchal rigidity, convulsive episodes, progressive decrease in the level of consciousness, lapsed into a coma, and developed respiratory failure and a picture of ARDS. She was put on non-invasive mechanical ventilation. A few days later, she was stabilized with the return to the sinus rhythm. Chest X-ray was initially reported as normal; few days into her ICU admission her chest X-ray and confirmed by a high-resolution CT scan demonstrated mild pulmonary edema (**Figure 1**), 2D-echo showed normal left ventricular function with 61% ejection fraction, abdominal ultrasound showed fatty liver and minimally enlarged spleen, and brain MRI was normal. Peripheral blood WBC was 4.2×10^3 but 9.0×10^3 towards recovery with a normal differential. Platelets reached a minimum of 31×10^3. They increased to normal values. Hemoglobin 12.8 gm/dl. Normal kidney function tests all throughout her hospitalization. liver function showed minimal transaminitis; ALT maximally 58 IU/L and AST 153 IU/L. Procalcitonin, COVID-19, hepatitis panel (A, B, C), anti-ccp, thin and thick blood films, INR, Aldolase, B-HCG, AMA, ENA, ANCA, C3, C4, cryoglobulins, ParvoB19, and reticulocytes all were normal. Buffy coat preparation showed intracellular cytoplasmic inclusions about 2 microns in diameter (**Figure 2**). CSF examination: total proteins 252.9 mg/dl, Glucose 98 mg/dl (serum glucose 176 mg/dl), RBC count 18 cell/mm^3, WBC 8 cell/mm^3, neutrophils 14%, lymphocytes 74%, monocytes 12%, no bacterial growth, CSF cytology showed lymphocytosis, negative rapid bacterial antigens (Latex). Pro-BNP was 4903. Gastrointestinal, neurological, rheumatological, hematological, and pulmonary, consultations were requested to address various issues, and an ophthalmology consultation was for significant conjunctival edema and horizontal nystagmus. The skin rash remained constant for a few days and faded later. In the ICU she was started on NGT Doxycycline 100 mg twice daily with an accelerated improvement. She showed a progressive improvement

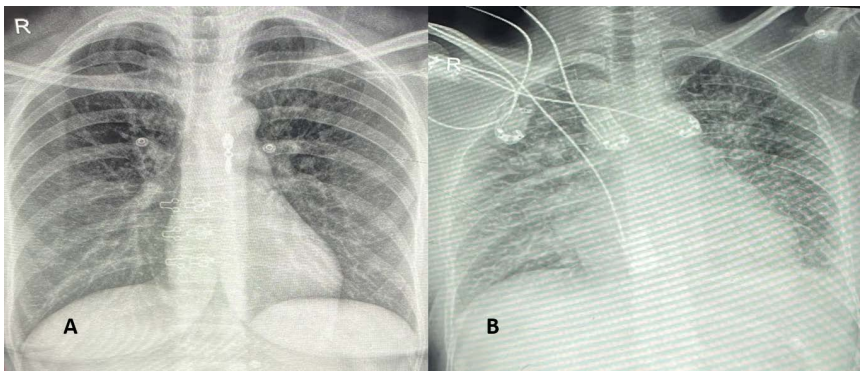

Figure 1. Chest X-rays of the patient on admission (A), and on her ICU admission (B) with non-cardiogenic pulmonary edema.

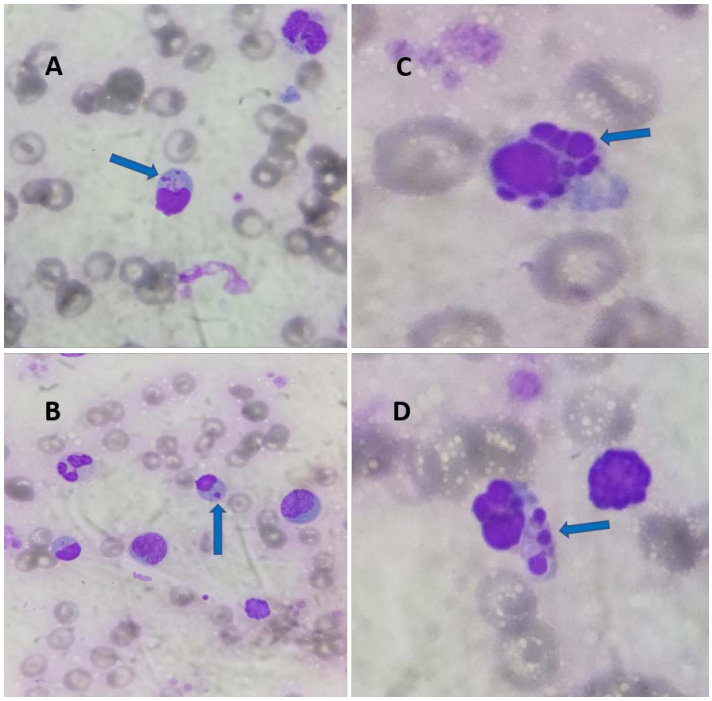

Figure 2. Buffy coat from the patient blood demonstrating Ehrlichia (A, B), and the mulberry appearance of the bacterial aggregate (C, D).

on Doxycycline; her breathing at room air was normal with normal O_2 saturation, steroids were prescribed for a short period and tapered rapidly, and she became conscious, alert, and oriented with residual myalgia and fatigue, and she was transferred to the ward. She was advised to continue a total of 2 weeks of Doxycycline. She returned to the outpatient clinic; she was ambulatory, though with a little wide base gait, and communicating well about her residual symptoms (*Note*: *her husband mentioned that there were two other similar cases in their village*, *one of them was a teenage girl who died in July* 2022, *and the other was a child who had a similar severe deterioration*, *he was admitted to an ICU and gradually improved after "antimicrobial" treatment. The ministry of health in Jordan was informed about launching an epidemiologic investigation*, *the other two patients might have been human Ehrlichiosis as well*).

3. Discussion

Our patient initially presented with non-specific symptoms of headaches, myalgias, tiredness, and fever. She was evaluated a couple of times by physicians, not suspecting a major medical illness, and missing an important piece of her history almost similar to two other cases in the isolated village that she lives in. A few days later she had presentations as a picture of suspected meningitis/encephalitis, seizures, coma, and skin rash including the palms and soles, which were enough to bring the attention of the treating team that infection other than the usual bacterial sepsis syndrome was taking place. A timely and early clinical suspicion helps in decreasing patients suffering, especially if the clinical picture does not

suggest a usual bacterial infection, and a constellation of symptoms as mentioned above was noted. Hitherto, initially, the differential diagnosis was wide, and many tests were requested to clarify the picture (see below), but the diagnosis was documented from the buffy coat examination, which demonstrated the intra-monocytic cytoplasmic bacteria and morulae with mulberry appearance (**Figure 2**), the buffy coat is helpful, and the diagnostic characteristics of HME/HGA are seen in about one-fourth of cases [5].

Worldwide, other tests for diagnosing HME/HGE are available, and those tests are not commonly used due to cost and the sporadic and rare occurrence of the infection; serology tests include the indirect fluorescent antibody (IFA) which is considered by USA-CDC as the reference standard, and enzyme-linked immunosorbent assays and Western immunoblotting [6]. However, the use of serological tests must be done with caution; in the first week it may return as negative, and it cannot differentiate the species. Also, IgG IFA assays should be performed on paired acute and convalescent serum samples collected 2 - 4 weeks apart to demonstrate evidence of a fourfold increase, or a seroconversion [7]. Detection of the organisms with polymerase chain reaction (PCR) assay is now becoming widely acceptable, negative results do not rule out the diagnosis, and PCR is helpful in the first week of illness. PCR is a promising method for diagnosing Ehrlichia early in the course of the infection [8].

Some patients suffering from Ehrlichiosis develop neutropenia, relative lymphopenia, and/or thrombocytopenia, and atypical lymphocytes, the CBC of our patient had minimal transient neutropenia on follow-up. Her CRP was elevated to 214 mg /dl on ICU admission then was normalizing, and ESR was normal all through her illness (maximum was 20). Our patient did not have hyponatremia, as reported in a review, where 40% of patients were found to have had a sodium level < 130 mEq/L [9]. Serum transaminases were moderately elevated in our patient (154 iu/dl), as reported in about 86% of patients [10]. A Lumbar puncture was necessary for the patient, especially with her neurological symptoms' presentation of fever, severe headache, seizures, and come.

Our patient was preceded by two cases (though we did not have enough data on both of them, similar in presentation and one died in another hospital, both were described as having suspected meningitis, skin rash, and ticks were suspected to be the cause of illness, the small village gossiped about ticks and tick-borne diseases that they had in their village). This piece of medical history must always draw attention to the fact that something different from the usual sepsis is happening.

Our patient was started on Doxycycline 100 mg twice daily. She had a swift response and recovered from her coma within 48 hours. Doxycycline was administered by NGT due to the unavailability of the parenteral form. She was discharged home a week later continuing her doxycycline for two weeks. A week later as an outpatient, she could walk, though with an unsteady gait, verbalizes, and could communicate her residual symptoms and concerns. Doxycycline can be administered intravenously in patients who are very sick and are unable to

tolerate oral medications, and orally in mild to moderate cases who can tolerate pills. The dose is usually 100 mg every 12 hours for a duration of 7 to 10 days or continued for 3 to 5 days after the resolution of fever in adults or 7 to 14 days in children. For patients who are intolerant or have a severe allergy to doxycycline, rifampin and chloramphenicol are alternative treatment options [11].

4. Conclusion

Human Ehrlichiosis may occur in Jordan likewise other parts of the world. Paying attention to the epidemiological history and patients' history, evolution of symptoms, and physical findings are strongly clued to enlist human Ehrlichiosis among the major differential diagnoses in such a scenario. Proper laboratory investigations aid in documenting the diagnosis.

Conflicts of Interest

No conflict of interest for all authors was declared.

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