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Acute Q fever with Secondary Hemophagocytic Syndrome: Case Report and Literatures Review

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Abstract

Hemophagocytic syndrome (HPS) is a rare and severe complication of acute Q fever. We describe one case of HPS in a 31-year-old man with fever, severe headache, and progressive thrombocytopenia. His condition met the modified Henter's criteria for HPS, and indirect immunofluorescence assay for *Coxiella burnetii* showed seroconversion with high titers of phase II IgM & IgG antibodies in convalescent serum. He received a 14-day course of levofloxacin because he had no response to doxycycline. This case suggests that HPS should be considered when hematological abnormalities develop in patients with acute Q fever, and that fluoroquinolones are an alternative therapy for doxycycline-refractory Q fever. (J Intern Med Taiwan 2015; 26: 363-368)

Key Words: Acute Q fever, Hemophagocytic syndrome, Fluoroquinolone

Background

Q fever, caused by *Coxiella burnetii*, is a zoonosis that has a variable presentation, ranging from asymptomatic seroconversion to severe fulminant hepatitis [1, 2]. Hemophagocytic syndrome (HPS) is a severe condition presenting with fever, splenomegaly, cytopenia, and histologic hemophagocytosis, and may be associated with malignancy, autoimmune disease, drug hypersensitivity reactions, and infections [3-6]. Among infections causing HPS, Q fever has seldom been described [3]. The Henter criteria and Imashuku criteria have been proposed for diagnosing primary HPS, but have not yet been evaluated in secondary HPS [7]. Although the diagnosis of HPS remains difficult, secondary HPS remains under-diagnosed.

We report one case of acute Q fever with a rare manifestation of secondary HPS.

Case presentation

A 31-year-old healthy man presented with fever, headache, and cough since 1 week. He denied any travel history and any history of exposure to animals. His headache characteristics were as follows: a visual analog score of 6-7/10, a duration of 1-2 hours, an onset to maximal intensity interval of seconds, a frequency of 2-3 times/day, aggravation by exercise, and relief with rest. The headache was not related to posture, cough, or exertion. The headache became more severe and frequent (2 times/day), without nausea or vomiting. He presented to our institute for further management because of poor response to initial treatment at a clinic. After admis-

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sion, his vital signs were as follows: blood pressure, 130/90 mmHg; body temperature, 39.8°C; pulse rate, 92/min; and respiratory rate, 20/min. His white blood cell count was 8,700/mm^3 (59% neutrophils, 21% lymphocytes, 11% monocytes, 7% eosinophils, and 2% basophils), hemoglobin level was 10.7 g/dL, and platelet count was 20,000/mm^3. Biochemistry examinations revealed glutamate-oxaloacetate transaminase level of 193 U/L, glutamic-pyruvic transaminase of 298 U/L, total bilirubin of 1.0 mg/dL (direct, 0.3 mg/dL), lactate dehydrogenase of 354 U/L, total cholesterol of 190 mg/dL, triglyceride of 111 mg/dL, blood urea nitrogen of 15 mg/dL, creatinine of 0.9 mg/dL, and C- reactive protein (CRP) of 7.0 mg/dL. The coagulation profiles included a prothrombin time of 12.1 seconds (control, 11.8 seconds; international normalized ratio [INR] = 1.3), a partial thromboplastin time of 40.6 seconds (control, 31.0 seconds), and fibrinogen level of 221 mg/dL. Oral doxycycline (100 mg) twice daily was prescribed for presumed atypical infection, especially rickettsiosis. Abdominal ultrasonography revealed mild he-patosplenomegaly. However, his fever and headache persisted despite 3 days of oral doxycycline therapy. Lumbar puncture was then performed, and the cerebrospinal fluid evaluations were within normal limits. Parenteral ceftriaxone (2000 mg every 12 hours) was added to treat clinically probable central nervous system infection and leptospirosis. Serologic tests for human immunodeficiency virus, toxoplasma, Epstein-Barr virus, cytomegalovirus, and viral hepatitis B and C were all negative. Furthermore, persistent symptoms and progressive bicytopenia (hemoglobin level of 8.0 g/dL and platelet count of 9,000/mm^3) were noted. Bone marrow examination revealed normal cellularity with an adequate number of megakaryocytes. The myeloid series (M) had good maturation but the erythroid series (E) was decreased, with an M/E ratio of 1.8. Macrophages containing numerous cytoplasmic red blood cells were observed (Figure 1). Further hematological tests revealed a prothrombin time of 14.1 seconds (control, 11.9; INR = 1.6), partial thromboplastin time of 49.7 seconds (control, 33.2), ferritin level of 5569 μg/L, fibrinogen level of 221 mg/dL, D-dimer level of 1400 ng/mL, and negative anti-nuclear and anti-cardiolipin antibodies. These results fulfilled the modified Henter's criteria for HPS [8]. Disseminated intravascular coagulation was also suspected. In addition, seroconversion for Q fever by indirect immunofluorescence assay revealed an IgG antibody titer of 1:640 and IgM antibody titer of 1:80 (cut-off titers were IgG 1:640 and IgM 1:80 according to the definition of the Taiwan CDC). Because his fever, headache, anemia, and thrombocytopenia persisted, we prescribed parenteral levofloxacin, 750 mg daily, discontinuing the doxycycline and ceftriaxone. Fever and headache subsided gradually within 5 days, and the platelet count and hemoglobin normalized. The patient was discharged 1 week later. He remained in a stable condition and had a normal platelet count after 14 days of levofloxacin therapy. He recovered well and remained well throughout the following one year. And, he did not develop chronic Q fever.

Discussion

To the best of our knowledge, this is the first reported case of this presentation for Q fever in

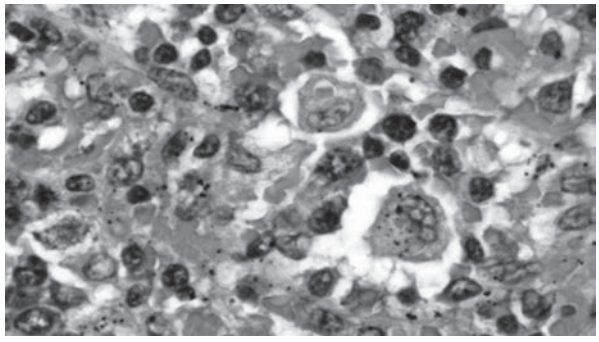

Figure 1. Microscopic findings of the bone marrow biopsy from our patient with Q fever and hemophagocytic syndrome. Macrophages containing numerous red blood cells in their cytoplasm were observed [Hematoxylin and eosin stain, ×1000].

central Taiwan, and the ninth reported case worldwide (Table 1, Appendix) [3, 9-12]. HPS is a rare and fatal complication of Q fever. The initial presentation of Q fever patients includes fever (100%), cough (77.2%), dyspnea (22.2%), and splenomegaly (66.7%) (Table 1). The reported platelet count ranged from of 3,000/mm^3 to 830,000/mm^3 (median 87,500/mm^3) (Table 1). Symptoms resolved after either tetracycline or doxycycline treatment (Table 1). Our case had a different presentation. His symptoms had a poor response to doxycycline treatment but responded to levofloxacin. We prescribed 2 weeks of levofloxacin therapy. Our experience suggests that fluoroquinolones may be a good alternative for doxycycline-refractory Q fever.

Table 1. Summary of clinical data from 9 patients with Q fever and associated secondary hemophagocytic syndrome

Variable	description for quantity
Demography	
Age, median (range)	44.3 (11-65)
Men	8 (8/9, 88.9%)
Clinical presentation	
Fever	9 (9/9, 100%)
Pulmonary involvement, cough	7 (7/9, 77.8%)
Pulmonary involvement, dyspnea	2 (2/9, 22.2%)
Splenomegaly	6 (6/9, 66.7%)
Laboratory data	
Neutrophils (×1000/mm^3), median (range)	3.5 (0.2-8.7)
Hb (g/dL), median (range)	10.6 (9-12)
Platelets (×1000/mm^3), median (range)	87.5 (3-830)
Ferritin (μg/L), median (range)	1000 (275-15000)
TG (mg/dL), median (range)	300 (110-440)
LDH (U/L), median (range)	832.5 (354-1089)
Fibrinogen (g/L), median (range)	221 (130-260)
D-dimer (ng/mL), (range)	(1400->6500)
CRP (mg/L), median (range)	19.6 (3-26.2)
Pathological data	
Histological hemophagocytic syndrome	9 (9/9, 100%)
Henter's criteria, median (range)	4 (3-5)
Imashuku's criteria, median (range)	3 (2-4)
Treatment (final regimen)	
Tetracycline group	6 (6/8, 75%)
Fluoroquinolone group	2 (2/8, 25%)
Additional therapy other than antibiotics	3 (3/8, 37.5%)
Outcome	
Survival	8 (8/8, 100%)

Abbreviation: CRP, C-reactive protein; Hb, hemoglobin; LDH: lactic dehydrogenase; TG: triglycerides.

The definitive diagnosis of HPS can be difficult, and requires the presence of five of eight of Henter's criteria, as well as histologic hemophagocytosis [8]. Although studies in secondary HPS are still lacking, these criteria remain widely used [12]. However, these criteria include natural killer cell activity and soluble interleukin 2 receptor levels, which are seldom checked in routine practice; hence, the use of Henter's criteria can make diagnosis of HPS more challenging. We believe this is a major reason why secondary HPS remains underdiagnosed.

Treatment of acute Q fever with doxycycline (100 mg per os twice daily for 14 days) is usually successful, and fluoroquinolones are also effective [2]. This case was successfully treated by levofloxacin after a poor response to doxycycline treatment. According to some studies, fluoroquinolones were more effective than doxycycline in treating Q fever [13]. Table 1 shows that most patients (6/8, 75%) received tetracycline-group antibiotics. Meanwhile, the drug of choice for acute Q fever varies in different geographic areas. Based on this case, we recommend that fluoroquinolones be considered the alternative drugs of choice for doxycycline-refractory cases of Q fever.

The prognosis of HPS depends on the underlying disease, but generally remains poor [14]. In the patients presented in Table 1, the outcome was good (survival, 8/8, 100%) for Q fever-associated HPS, with most cases (5/8, 62.5%) receiving no additional treatment other than antibiotics. Our patient recovered well without HPS-specific treatment.

Conclusions

We propose that HPS should be considered when hematological abnormalities develop among patients with acute Q fever, and fluoroquinolones can be the alternative therapy for doxycycline-refractory Q fever.

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急性Q熱合併續發性噬血症候群：病例報告與文獻回顧

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摘　要

噬血症候群，是急性Q熱罕見的一種嚴重的併發症。我們報告一例３１歲的男性，發生發燒，畏寒，頭痛，咳嗽，與血小板低下，依照Henter標準疾病吻合的嗜血症候群的診斷，並且血清學確認是急性Q熱。在doxycycline治療反應不佳情形下，病患接受14天的levofloxacin治療後，順利康復出院。我們建議，急性Q熱病患出現血液學異常的現象需要將噬血症候群列入鑑別診斷，此外，在doxycycline治療反應不佳情形下，fluoroquinolones可以考慮為替代性治療。

Appendix: Characteristics of 9 patients with Q fever and associated secondary hemophagocytic syndrome

				Criteria			Clinical presentation						Laboratory data									Therapy		Outcome
Patient	Author	Publication year	Country	HPS	Henter's criteria	Imashuku's criteria	Age/ sex	Fever	Skin [1]	Lung [2]	Heart [3]	SMG	Neutrophils(×1000/mm^3)	Hb(g/dL)	Platelets(×1000/mm^3)	Ferritin(μg/L)	TG(mg/dL)	LDH(U/L)	Fibrinogen(g/L)	D-dimer (ng/mL)	CRP(mg/dL)	backbone regimen	additional anti-HPS therapy	Survival
1	This case	2015	Taiwan	Yes	4	4	31/M	Yes	No	No	No	Yes	8.7	10.7	20	5569	111	354	221	1400	7	FQ	Neg	Yes
2	Lecronier M	2013	France	Yes	4	3	65/M	Yes	No	Dysp, cou	No	Yes	4.46	8.2	338	1457	230	592	NA	NA	26.2	TC	IVIG	Yes
3	Lecronier M	2013	France	Yes	4	4	30/M	Yes	No	Cou	No	No	1.7	11	128	15 000	440	2301	NA	NA	24.4	TC	IVIG	Yes
4	Lecronier M	2013	France	Yes	4	3	60/F	Yes	No	Cou	No	No	1.52	11.1	87	510	300	665	260	NA	3	TC	CS	Yes
5	Lecronier M	2013	France	Yes	4	3	46/M	Yes	No	No	No	No	2.7	14	88	1000	300	NA	NA	NA	19.6	TC	Neg	Yes
6	Chen TC	2006	Taiwan	Yes	4	4	26/M	Yes	No	Cou	NA	Yes	4.5	9	3	275	110	1000	NA	>6500	7	FQ	Neg	Yes
7	Lee HC	2002	Taiwan	Yes	3	3	63/M	Yes	NA	Cou	NA	Yes	NA	12	830	NA	NA	NA	NA	NA	NA	TC	Neg	Yes
8	Hufnagel M	1995	Germany	Yes	5	4	11/M	Yes	NA	Cou	No	Yes	0.2	9.9	54	NA	300	1089	130	NA	21	TC	NA	Yes
9	Estrov Z	1984	Canada	Yes	3	2	51/M	Yes	NA	Cou, dysp	NA	Yes	4	11.7	86	NA	NA	NA	NA	NA	NA	NA	NA	NA

Notes: [1]Cutaneous involvement; [2]Pulmonary involvement; [3]Endocarditis

Abbreviation : CRP, C-reactive protein; CS, Corticosteroids; Cou, cough; dysp, dyspnea; F, female; Hb, hemoglobin; HPS, hemophagocytic syndrome; SMG, splenomegaly; LDH, lactate dehydrogenase; IVIG, Intravenous immunoglobulin ;M, male; NA, not available; TG, triglycerides.