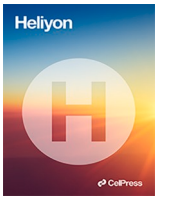
Heliyon 10 (2024) e24538

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

Severe Jarisch-Herxheimer Reaction (JHR) in a leptospirosis patient: A case report

Ruo-Yan Zhao [a,c], Meng-Die Liu [b,c], Ying-Xin Lin [c], Lei Huang [c,*]

[a] Hubei University of Medicine, Shiyan, 442000, Hubei Province, China
[b] Shenzhen University, Shenzhen, 518000, Guangdong Province, China
[c] Intensive Care Unit, Peking University Shenzhen Hospital, Shenzhen, 518000, Guangdong Province, China

ARTICLE INFO

Keywords:
Leptospirosis
Jarisch-Herxheimer reaction
Acute respiratory distress syndrome
Acute renal failure
Case report

ABSTRACT

Leptospirosis is a zoonosis that is related to potential respiratory, renal, neurological, and cardiovascular failure. At present, antibiotics are the recommended treatment, but due to the underlying cause of the disease, they may induce the Jarisch-Herxheimer reaction (JHR) within 24 hours. At the same time, we speculate that JHR may aggravate the natural course of leptospirosis. Considering that there are few available reports on this event, we will share a case of pulmonary hemorrhagic leptospirosis, where antibiotic treatment is suspected to have triggered the JHR. This report is expected to improve clinical attention to the relationship between leptospirosis and JHR.

1. Introduction

JHR is an immune response that was initially reported after the use of antibiotics for treating syphilis [1]. Later, it was found that this reaction also occurred in leptospirosis, Lyme disease, and relapsing fever. Among them, the probability of JHR occurring in leptospirosis was the lowest, only 9 %, mainly depending on the antibiotics used. JHR usually presents with fever, chills, stiffness, nausea and vomiting, headache, tachycardia, hypotension, hyperventilation, flushing, myalgia, and deterioration of skin lesions. However, severe cases may also have worsening symptoms, hepatic insufficiency, acute renal injury, acute respiratory distress, and pulmonary hemorrhage. Its progress may be closely related to the selection and duration of antibiotic use, as well as the biological load in vivo. Please note that the diagnosis of JHR was not supported by any biological markers. Additionally, the definition of JHR was not uniform, so most of the cases presented a genuine JHR, but some might have had a clinical aggravation related to the spirochetal disease regardless of the antibiotherapy. We recommend that patients receiving penicillin or other antibiotics for the management of leptospirosis should be monitored early after the initiation of treatment to prevent any detrimental effects of a potential JHR.

2. Case presentation

A 64-year-old man presented to the Emergency Department with a complaint of hemoptysis, fever, and difficulty exhaling that stretched for five days. The patient had previous history of hypertension and field work. Upon admission, physical examination

* Corresponding author. Intensive Care Unit, Peking University Shenzhen Hospital, No. 1120, Lianhua Road, Futian District, Shenzhen, Shenzhen, 518000, Guangdong Province, China.
E-mail address: zhaozoe0324@163.com (L. Huang).

https://doi.org/10.1016/j.heliyon.2024.e24538
Received 27 July 2023; Received in revised form 6 January 2024; Accepted 10 January 2024
Available online 13 January 2024

revealed a low-grade fever (37.8 °C), dyspnea (22/min) and blood pressure of 144/88 mmHg. Based on clinical manifestations, laboratory tests (Table .1), and chest high-resolution CT (Fig. 1), the proposed diagnosis is severe pneumonia, respiratory failure, multiple organ failure, and septic shock. On the first day of admission, the patient was administered on Cefoperazone-Sulbactam (3.0g q12 IV) and oxygen therapy. But six hours after the administration of treatment, the clinical manifestations of patient were worsened compared to before (T:40 °C, RR:28/min, BP:80/50 mmHg). The patient was immediately intubated, vigorously resuscitated with fluids and vasopressors (Epinephrine 0.6 μg/kg*min), and admitted to the intensive care unit with an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 33.

After being received mechanical ventilation and pressor drugs, the patient's vital signs were still unstable (T: 36.5 °C, RR: 35/min, BP: 79/54 mmHg), arterialblood gas revealed type II respiratory failure (Table .1), and chest X-ray suggested diffuse inflammatory changes in both lungs (Fig. 2). In order to evaluate the condition of the patient, we performed a fibronchoscopy examination, which showed that copious amount of bloody sputum in each lung segment. Therefore, for purpose of excluding the infection of special pathogens, we sent blood samples for Next Generation Sequencing (mNGS testing, Dinfectome, 7/17Nanjing, China, Illumina Nextseq 550DX platform). On the second day of admission, after assessing the risk of bleedingand coagulation, the patient received network vein extracorporeal membrane oxygenation (VV-ECMO) for improving the patient's refractory respiratory failure; The antibiotic was upgraded to a special level antibiotic meropenem (2.0g q8h IV); With the increase of blood creatinine and the symptom of anuria, the patient received early renal replacement therapy. On the third day of admission, according to the mNGS results indicating leptospira infection (sequence number 8864), the antibiotic was adjusted to penicillin 400000U q6h and the patient underwent VV-ECMO evaluation. After 7 days of the above treatment, the patient withdrew from the ventilator on the 10th day (Fig. 3) and discharged on the 13th day. He was doing very well at the 6-month follow-up (Fig. 4). The individual was ultimately diagnosed with leptospirosis, severe pneumonia, acute kidney injury, and acute liver injury.

3. Discussion

This case report describes the complicated history of leptospirosis, with suspected to have JHR after antibiotic treatment. The report also reiterates the successful treatment of the condition with ECMO, after a state of severe pulmonary hemorrhage. The patient was administered with strong antibiotics when he was admitted to the hospital. After mechanical ventilation, and continuous renal replacement therapy, his respiratory and circulatory conditions did not improve but even worsened, which is difficult to explain. Through literature search, we realized that antibiotics related to the development of JHR not only include penicillins, tetracyclines and erythromycin, but also newer antimicrobial agents such as cephalosporins, levofloxacin, ciprofloxacin, clarithromycin, meropenem, and azithromycin can also cause JHR [1]. To prove the relationship between leptospirosis and JHR and predict the characteristics of patients with severe types, we searched and reviewed the presentation of five adults with pulmonary hemorrhagic leptospirosis, and found that they all showed aggravation of existing symptoms or the occurrence of new symptoms that cannot be explained by the progression of the disease [2–6]. However, they survived after active symptomatic treatment (Table 2). To sum up, we hold the view that JHR was involved in the case that we reported in this study.

JHR is an acute, self-limiting disease, whose treatment is predominantly supportive [7]. The patient may have fever, chills, decreased blood pressure, altered consciousness, and other shock symptoms within a few hours after the administration of antimicrobial agents in spirochete disease. These symptoms are serious enough to cause a devastating incidence rate and mortality [8]. At present, extension literature search suggested that the selection and duration of antibiotics for leptospirosis, as well as the in vivo

Table 1
Laboratory examination results after admission and antibiotic usage.

Variable	1st	2nd	3rd	5th	7th	9th	11th
ANTIBIOTIC	Cefoperazone Sulbactam	Meropenem	Penicillin	Penicillin	Penicillin	Penicillin	/
WBC(*10^9)	12.32	20.95	21.01	13.27	20.68	16.96	15.29
NEU(*10^9)	11.10	17.92	16.89	11.16	16.84	13.29	13.30
LYM(*10^9)	0.30	1.09	1.04	0.97	2.60	2.46	0.99
MONO(*10^9)	0.79	1.88	3.02	1.11	1.18	1.11	0.78
PLT(*10^9)	25	12	32	153	72	71	57
HGB(g/L)	96	52	57	92	95	100	94
PCT(ng/mL)	1.47	75.8	>100	>100	35.20	16	3.84
IL-6(pg/mL)	2895	>5000	761	80	68.9	54.40	167
pH	7.17	6.94	7.08	7.51	7.57	7.51	7.38
PO_2(mmHg)	67	93	59	83	84	77	80
PCO_2(mmHg)	49	56	102	39	39	42	42
OI(mmHg)	140	93	59	104	280	154	229
Lac(mmHg)	/	10.09	3.1	2	2.4	1.4	1.3
ALT(U/L)	92	/	464	156	102	59	37
Cr(umol/L)	422	/	236	215	199	251	146
eGFR(ml/min)	12	/	24.2	27	29.7	22.4	43.2

WBC: White blood cell count; NEU: Absolute neutrophil count; LYM: Absolute lymphocyte count; MONO: Absolute value of monocytes; PLT: Platelets; HGB: Hemoglobin; PCT: Procalcitonin; IL-6: Interleukin; PH: Potential of hydrogen; PO_2: Partial pressure of oxygen; PCO_2: Partial pressure of carbon oxygen; OI: Oxygenation index; Lac: lactic acid; ALT: Alanine transaminase; Cr: Creatinine; eGFR: Estimated glomerular filtration rate.

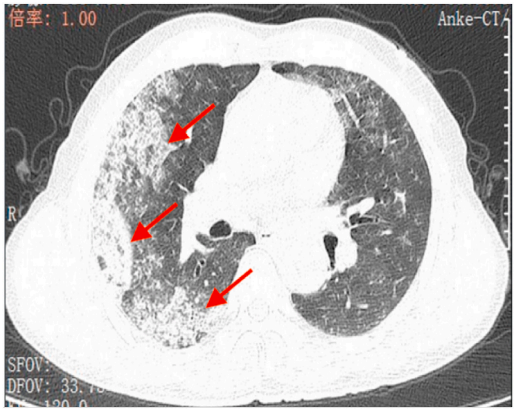


Fig. 1. Chest high-resolution CT images on admission. Both lungs are scattered with exudative lesions (At the red arrow) . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

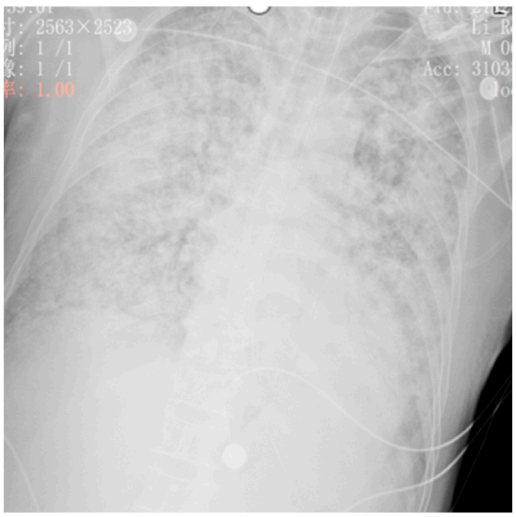


Fig. 2. Chest X-ray captured on the first day of admission.

biological load, may be closely related to the progression of JHR response. In a randomized controlled study by Nadelman et al. it was found that the faster the bactericidal effect of the selected antibiotic in the treatment of early spiral infection, the more likely it is to accelerate the progression of JHR [9]. Knaack et al. found that penicillin clears spirochetes in the blood at a slower rate, resulting in a lower severity of JHR [10]. Gilles Guerrier et al. conducted a retrospective study on the risk factors for JHR in 262 confirmed patients with leptospirosis in New Caledonia and Futuna. They found that the Australian serogroup of leptospirosis and delayed antibiotic treatment were potential risk factors for the occurrence and development of JHR [11]. Chia Jui Yang et al. conducted a prospective survey on the risk factors for JHR response in 240 syphilis patients receiving penicillin treatment and found that for every 2-fold increase in high rapid plasma reactive protein (RPR) titer, the risk of JHR increased by 19 % [12]. This indicates that in the early stages of syphilis, when patients receive fungicide treatment, the higher the load of spirochetes, the faster the progression of JHR response. Despite recent advances in the medical field, the exact mechanism of JHR is still unclear and is thought to be multifactorial. It has been reported that JHR leads to the increase of inflammatory cytokines, including interleukin-6 (IL-6), IL-8, IL-1β, and tumor necrosis factor-alpha (TNF-α). TNF-α, IL-1, and IL-6 can activate the coagulation system, which may be related to clinical bleeding, especially severe pulmonary hemorrhagic syndrome [13]' and the coagulation activation that is observed in severe leptospirosis [14]. It is worth noting that the inflammatory cell infiltration antagonist such as tocilizumab was proposed to prevent and ameliorate the JHR [1,15,16], but has not been clinically verified in leptospirosis. Steroids and an opioid analgesic (meptazinol) can reduce the severity of JHR [15]. Currently, some doctors have used this treatment to prevent JHR, but it is unclear whether it is effective enough. Moreover, methylprednisolone can reduce the mortality of patients with severe leptospirosis, except in cases where patients have multiple organ dysfunction and comorbidity [17]· Considering that the study of JHR is a transient clinical event, no specific test can be used to diagnose the disease. In addition to drug prevention, we recommend that patients receiving penicillin or other antibiotics for the management of leptospirosis be monitored early, after initiation of the treatment to prevent any detrimental effects of a potential

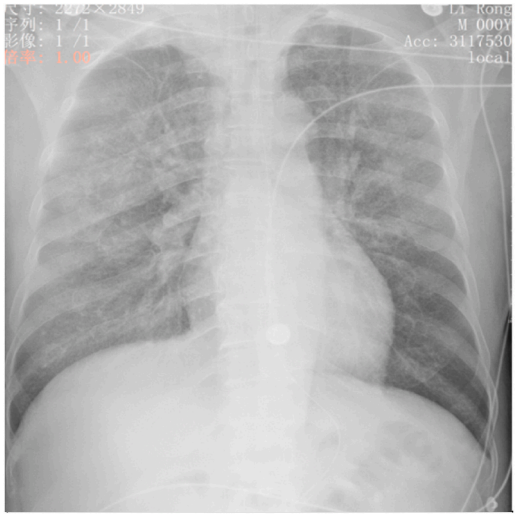


Fig. 3. Chest X-ray captured on the tenth day of admission.

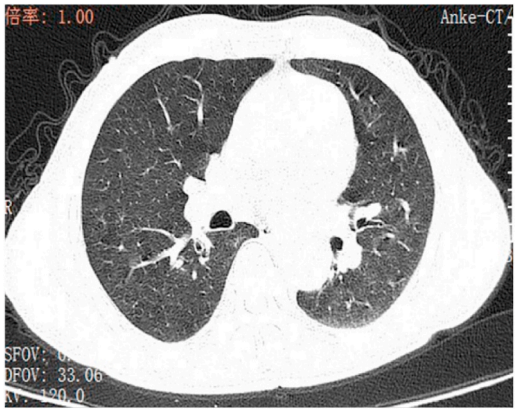


Fig. 4. Chest high-resolution CT images at follow-up. The exudate foci in the lungs are basically absorbed and disappear.

Table 2
Jarisch-Heirxheimer reaction after admistration of antibiotics for the treatment of leptospirosis.

Country	Age	Antibiotic	Delay before JHR	Symptoms	Treatment measures	Ooutcome
Japanese	42	ceftriaxone sodium	48 hours	respiratory worsened pulmonaryalveolar hemorrhag	Continue antibiotic treatment	Survive
Turkey	21	ceftriaxone	24 hours	hyperpyrexia headache, widespread myalgia, and weakness	isopropyl alcohol	Survive
American	28	doxycycline and ceftriaxone	1.5 hours	Pulmonary deterioration hemodynamic instability	Nasal catheter oxygen inhalation norepinephrine	Survive
American	41	doxycycline and piperacillin/ tazobactam	4 hours	Tachycardia Respiratory distress	steroids and diphenhydramine Endotracheal intubation continuous veno-venous hemofiltration	Survive
Japanese	39	ceftriaxone and metronidazole	<24 hours	hemodynamic instability progressive respiratory failure renal failure	mechanical ventilation v-vECMO hemofiltration	Survive

JHR.

4. Conclusion

In summary, JHR is a known complication of leptospirosis. It is our hope that sharing this case will improve the clinical understanding of the relationship between JHR and leptospirosis. Currently, new treatment or prevention strategies, such as anti-tumor necrosis factor antibodies, are promising, but they have not been explored in the management of leptospirosis. The link between JHR and organ failure or death is not yet clear, and our case cannot be promoted to the entire population. Therefore, large-scale research is needed to design specific monitoring for identifying the incidence rate and impact of JHR, together with the severity and incidence rate of various antibiotics. This work will help to better estimate the potential adverse effects of antibiotics on leptospirosis and provide information for future management guidelines.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Data availability

The authors will supply the relevant data in response to reasonable requests.

CRediT authorship contribution statement

Ruo-Yan Zhao: Writing – original draft, Data curation. **Meng-Die Liu:** Writing – original draft, Data curation. **Ying-Xin Lin:** Validation, Supervision, Project administration, Methodology. **Lei Huang:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Dhakal, E. Sbar, Jarisch-Herxheimer Reaction, StatPearls Publishing, Treasure Island (FL, 2023.
[2] A. Maier, R. Kaeser, R. Thimme, T. Boettler, Acute pancreatitis and vasoplegic shock associated with leptospirosis - a case report and review of the literature, BMC Infect. Dis. 19 (1) (2019) 395, https://doi.org/10.1186/s12879-019-4040-1.
[3] P. Pothuri, K. Ahuja, V. Kumar, S. Lal, T. Tumarinson, K. Mahmood, Leptospirosis presenting with rapidly progressing acute renal failure and conjugated hyperbilirubinemia: a case report, Am J Case Rep 17 (2016) 567–569.
[4] T. Kupferman, M.P. Coffee, B.J. Eckhardt, Case report: a cluster of three leptospirosis cases in a New York city abattoir and an unusual complication in the index case, Am. J. Trop. Med. Hyg. 97 (6) (2017) 1679–1681, https://doi.org/10.4269/ajtmh.17-0545.
[5] H.J. Wang, G.Z. Chen, C.J. Zhou, Y. Fu, L.N. Yao, Veno-venous extracorporeal membrane oxygenation successfully treated a case of severe pulmonary hemorrhage caused by leptospirosis, BMC Infect. Dis. 20 (1) (2020) 794, https://doi.org/10.1186/s12879-020-05518-1.
[6] T. Cantwell, A. Ferre, N. Van Sint Jan, R. Blamey, J. Dreyse, C. Baeza, R. Diaz, T. Regueira, Leptospirosis-associated catastrophic respiratory failure supported by extracorporeal membrane oxygenation, J. Artif. Organs 20 (4) (2017) 371–376, https://doi.org/10.1007/s10047-017-0998-x.
[7] G.R. Belum, V.R. Belum, S.K. Chaitanya Arudra, B.S. Reddy, The Jarisch-Herxheimer reaction: revisited, Trav. Med. Infect. Dis. 11 (4) (2013) 231–237, https://doi.org/10.1016/j.tmaid.2013.04.001.
[8] S. Takamizawa, H. Gomi, Y. Shimizu, H. Isono, T. Shirokawa, M. Kato, Leptospirosis and jarisch–herxheimer reaction, QJM: An International Journal of Medicine 108 (12) (2015) 967–968, https://doi.org/10.1093/qjmed/hcv077.
[9] B. Robert, M. Nadelman, W. Steven, M.D. Luger, M.D. Elliot Frank, Wisniewski Michael, Jeffrey J. PhD, PhD. Collins, P. Gary, M.D. Wormser, Comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease, Ann. Intern. Med. 117 (4) (1992) 273–280, https://doi.org/10.7326/0003-4819-117-4-273%m1637021.
[10] R.H. Knaack, L.J. Wright, C.S. Leithead, T.G. Kidan, J.J. Plorde, Penicillin vs. tetracycline in the treatment of louse-borne relapsing fever. A preliminary report, Ethiop. Med. J. 10 (1) (1972) 15–22.
[11] G. Guerrier, P. Lefèvre, C. Chouvin, E. D'Ortenzio, Jarisch-herxheimer reaction among patients with leptospirosis: incidence and risk factors, Am. J. Trop. Med. Hyg. 96 (4) (2017) 791–794, https://doi.org/10.4269/ajtmh.16-0457.
[12] C.J. Yang, N.Y. Lee, Y.H. Lin, H.C. Lee, W.C. Ko, C.H. Liao, C.H. Wu, C.Y. Hsieh, P.Y. Wu, W.C. Liu, Y.C. Chang, C.C. Hung, Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the hiv infection epidemic: incidence and risk factors, Clin. Infect. Dis. 51 (8) (2010) 976–979, https://doi.org/10.1086/656419.
[13] D.A. Haake, P.N. Levett, Leptospirosis in humans, in: B. Adler (Ed.), Leptospira and Leptospirosis, Springer Berlin Heidelberg, Berlin, Heidelberg, 2015, pp. 65–97.
[14] J.F. Wagenaar, M.G. Goris, D.L. Partiningrum, B. Isbandrio, R.A. Hartskeerl, D.P. Brandjes, J.C. Meijers, M.H. Gasem, E.C. van Gorp, Coagulation disorders in patients with severe leptospirosis are associated with severe bleeding and mortality, Trop. Med. Int. Health 15 (2) (2010) 152–159, https://doi.org/10.1111/j.1365-3156.2009.02434.x.
[15] M.W. Pound, D.B. May, Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions, J Clin Pharm Ther 30 (3) (2005) 291–295, https://doi.org/10.1111/j.1365-2710.2005.00631.x.
[16] D. Fekade, K. Knox, K. Hussein, A. Melka, D.G. Lalloo, R.E. Coxon, D.A. Warrell, Prevention of Jarisch-Herxheimer reactions by treatment with antibodies against tumor necrosis factor alpha, N. Engl. J. Med. 335 (5) (1996) 311–315, https://doi.org/10.1056/nejm199608013350503.
[17] S.A. Kularatne, B.D. Budagoda, V.K. de Alwis, W.M. Wickramasinghe, J.M. Bandara, L.P. Pathirage, G.R. Gamlath, T.J. Wijethunga, W.A. Jayalath, C. Jayasinghe, V. Pinto, P. Somaratne, P.V. Kumarasiri, High efficacy of bolus methylprednisolone in severe leptospirosis: a descriptive study in Sri Lanka, Postgrad Med J 87 (1023) (2011) 13–17, https://doi.org/10.1136/pgmj.2009.092734.