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CASE REPORT

A Case of Hemophagocytic Lymphohistiocytosis Secondary to Ralstonia Solanacearum Infection

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SUMMARY

Background: **Hemophagocytic lymphohistiocytosis (HLH), as known as Hemophagocytic syndrome (HPS), is deemed to a severe clinical syndrome caused by excessive human being immune system activation. Bacteria of Ralstonia genus is a non-fermentative, gram-negative bacillus and also in the category of human opportunistic pathogenic bacteria. In this article, authors report a rare case of Hemophagocytic lymophohistiocytosis which probably was triggered by Ralstonia solanacearum (R. solanacearum) infection.**
Methods: **Hematologic investigation, biochemical examination, high throughput genetic test for infectious agents and bone marrow puncture.**
Results: **The patient achieved complete remission and no signs of relapse have as yet been found.**
Conclusions: **The bacteria of Ralstonia genus merely infect humans, and there were no reports about the infection of R. solanacearum in humans and secondary HLH. The prognosis of the patient in this case was very good. This result, we think shows that the relationship between HLH and R. solanacearum infection should be taken into the diagnosis process. Recognition of this will promote the correct diagnosis in clinical work.**
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KEY WORDS

hemophagocytic lymphohistiocytosis (HLH), Ralstonia solanacearum (R. solanacearum), infection

CASE PRESENTATION

A 41-year-old man was admitted to the emergency of our hospital on December 1, 2017, presented with 2 weeks history of pyrexia (the maximum body temperature was 39.5°C) and jaundice. He was otherwise healthy and denied specific familial medical history. Upon physical examination, the patient showed apparent jaundice in skin and scleras, and distended abdomen. Epigastric tenderness and rebound tenderness were positive in this patient. We then examined the blood test, biochemistry, liver function, lactate dehydrogenase, ferritin, nature killer cell activity, soluble CD25 (sCD25), and so on, shown in Table 1. Results of peripheral blood cultures were negative three times. Contrast-enhanced computed tomography (CT) of the chest

Table 1. The blood test of the patient.

Lab items	Day 1	Day 8	Day 18	Day 33	3 Months	Reference value
WBC (10^9/L)	6.34	3.87	13.67	3.24	4.92	3.5 - 9.5
* HGB (g/L)	101	64	76	92	127	130 - 175
* PLT (10^9/L)	165	398	400	215	202	100 - 350
* Neu# (10^9/L)	4.7	3.29	12.37	1.48	2.48	1.8 - 6.3
Aspartate aminotransferase (U/L)	157	45	27	27	29	15 - 40
Alanine aminotransferase (U/L)	134	47	82	62	32	3 - 35
Total bilirubin (μmol/L)	630	448.3	56.9	21	12.6	4.0 - 23.9
Direct bilirubin (μmol/L)	487	340.6	54.9	16.8	4.8	0 - 6.8
* Triglyceride (mmol/L)	6.54	4.73	0.98	1.66	1.42	0.78 - 1.92
* Ferritin (ng/mL)		> 1,650	749.3	1,157	714.6	22 - 322
C-reactive protein (mg/L)	135.9	76,2	1.1			0 - 6
Procalcitonin (ng/mL)	2.24	1.87				< 0.05
* sCD25 (pg/ml)		7,641				< 2,400
* Nature Killer cell activity		14.54%				≥ 15.1%

The items with * are diagnosis conditions of HLH, and we commenced HLH-94 scheme on day 9.

Table 2. The HLH associated familial genes of the patient.

Chrom position	Gene Sym	Coding region position	Type
chr10:72358577	PRF1-Exon3	c.900C>T(p.His300His)	synonymous mutation
chr19:7706656	STXBP2-Exon7	c.495C>T(p.Arg165Arg)	synonymous mutation
chr19:7711221	STXBP2-Exon16	c.1443T>C(p.Asp481Asp)	synonymous mutation
chr19:7712277	STXBP2-Exon18	c.1576A>G(p.He526Val)	missense mutation

and abdomen demonstrated hepatosplenomegaly and bilateral pneumonia. Positron Emission Computed Tomography (PET/CT) test showed that systemic reactive metabolism was slightly active and excluded possibilities of hypermetabolic tumors. From bone marrow puncture, about 1% abnormal phagocytic cells were found in the smear. HLH associated familial genes of this patient were checked, and the result was shown in Table 2. The blood specimen was sent for high throughput genetic testing for infectious agents. The report showed significant elevated copies of the gene sequence of R. solanacearum. Besides, the test of blood clotting function, autoimmune disease associated factors, DNA quantitative determination of cytomegalovirus and Epstein-Barr virus, and parasite detection were within reference values. Considering the presence of pneumonia in the patient, we empirically treated with antibiotics, including imipenem and cilastatin sodium, fluconazole, oseltamivir phosphate, cefoperazone sodium and sulbactam sodium, tigecycline. The diagnosis of HLH was based on HLH-2004 diagnostic criteria and the patient was treated with HLH-94 scheme accordingly. The therapy protocol was dexamethasone daily with 10 mg per square meter for 2 weeks, 5 mg per square meter for 2 weeks, 2.5 mg per square meter for 2 weeks, 1.25 mg per square meter for 1 week and tapered and discontinued during 1 week, and etoposide 0.1g twice a week for 2 weeks, 0.1g once a week for the next 6 weeks. The patient was also given liver and stomach mucous membrane protection medicines. After 8-weeks of active treatment, positive performances of physical examination and clinical presentations of the patient had disappeared and the parameters of hematological and biochemical tests were gradually normalizing (shown in Table 1).

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) was first described by Bodley R. Scott and Bobb-Smith in 1939 as "Histiocytic medullary reticulosis" (HMR) [1]. After a long period of research, HLH is defined as a class of life-threatening clinical syndromes caused by overactivation of the human immune system. By etiology, HLH usually is classified into two categories. Primary HLH was used to denote syndromes in patients who have explicit pathogenic genic mutations or with positive family history. Secondary HLH was used to denote manifestations of syndrome secondary to some diseases, such as infections, malignancies, toxicosis, and autoimmune diseases [2]. The syndrome with unknown primary cause is still regarded as secondary HLH in patients who have no currently known pathogenic gene confirmed [3]. The patient in this case had fever, splenomegaly, elevated fasting triglycerides and ferritin, descendant nature killer cell activity, increased level of sCD25 and hemophagocytosis in bone marrow. So, this case met the diagnosis of HLH-2004 diagnostic criteria [4]. There was literature showing that some mutation loci of the STXBP2 gene are possibly correlated with the HLH incidences of Chinese population [5]; however, by searching the current databases (HGMP pro, Pubmed, 1,000 Genomoes , dbSNP and Exac), these mutation loci of our patient were classified as Single Nucleotide Polymorphisms (not pathogenic) or synonymous mutation (no amino acid changes). Therefore, the diagnosis of secondary HLH was still our first consideration. HLH-94 protocol is usually the first choice for the treatment of HLH [6,7]. Thus, the patient finished the treatment course of HLH-94 protocol, and good prognosis had been achieved and no signs of relapse were found within 8 months after treatment.

Ralstonia solanacearum, originally called Bacillus solanacearum, is a non-fermentative gram-negative bacillus that can cause bacterial wilt of solanacearum in potato, tomato and other solanaceae [8], identified by Smith in 1896 [9]. In the long research and argument that followed, R. solanacearum was classified as another new genus Ralstonia containing five species, and renamed Ralstonia solanacearum [10]. This strain of bacteria has a wide distribution and influence on a variety of crops, but there was no report on the impact on humans or animals. However, the Ralstonia pickettii (R. pickettii) that belongs to the same genus with R. solanacearum, has been occasionally reported as a rare opportunistic pathogen of nosocomial infection [11]. According to previous reports, it is characterized by atypical clinical features, insufficient experience in diagnosis and treatment [12], mainly causing pneumonia [13], sepsis [14], and often more serious diseases. The result of the drug sensitivity test showed that most of isolated bacteria were sensitive to cefoperazone sodium and sulbactam sodium, sulfamethoxazole-trimethoprim, ciprofloxacin, but lacked regularity in sensitivities to carbapenems and aminoglycosides [15]. In our case, the high throughput genetic test showed a significantly elevated number of copies of the gene sequence of Ralstonia solanacearum, indicating infection by this bacterium. Unfortunately, the exact bacteria were not isolated from blood cultures. However, with empirical anti-infection treatment, the symptoms of infection, inflammatory indicators, and lung imaging showed significant improvement. In the absence of effective direct evidence of pathogens by conventional means, the detection technology helped us to identify pathogens and then guided the use of drugs, which is of great significance in promoting the outcome of patients' disease.

CONCLUSION

In conclusion, we report a rare case of secondary HLH, probably following infection by R. solanacearum, with good curative efficacy. Due to the lack of direct etiological evidence and literature support, we are still unable to confirm the pathogen of the infection. However, the rare human infection of this bacterium should still attract the attention of physicians and clinicians.

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Declaration of Interest:
The authors state that there are no conflicts of interest to disclose.

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