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Case Report

Challenges of the treatment of pediatric hepatosplenic bartonellosis: case report and literature review

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Abstract

The hepatosplenic (HS) form of cat scratch disease (CSD) is rarely seen; however, management of the treatment is challenging for clinicians. Monotherapy or combination regimens may be preferred based on severity of cases. Along with that, there are uncertainties as to the combination and duration of antibiotics effective against the microorganisms. In this report, a 12-year-old girl diagnosed with HS-CSD and unresponsive to primary treatment with macrolide group antibiotic was presented. The patient had liver findings compatible with CSD, confirmed radiologically and pathologically, and *Bartonella henselae* indirect immunofluorescence assay IgG was positive at 1/2048 titre. A combination therapy for six months with doxycycline and rifampicin was initiated, and the patient was successfully treated. The preference for monotherapy or combination regimen in HS-CSD is predominantly determined by the clinician according to the severity of the patient's clinical findings. The effectivity of antimicrobial regimen in HS-CSD requires further investigation.

Key words: Bartonellosis; hepatosplenic; treatment.

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Introduction

Bartonellosis, also known as cat scratch disease (CSD), most commonly associated with *Bartonella henselae* is an acute self-limiting disease that occurs as a result of scratching or biting by an infected cat [1]. Although it is seen especially during childhood and early adulthood, infection can be seen at any age [1,2]. The disease is mostly in the form of regional lymphadenopathy associated with papule in the scratched skin area. Rarely, disseminated bartonellosis with organ involvements such as bone, heart, liver, spleen and central nervous system can be seen [1,3,4]. The diagnosis of the disease is usually made by imaging methods and serological tests in clinically suspected cases [3]. In disseminated disease, histopathologic diagnosis may be required by tissue sampling to exclude other reasons [2,3]. The vast majority of patients recover spontaneously without specific treatment [3,4]. There are limited studies about the effectiveness of treatment in patients requiring antibiotherapy [4]. This infection still lacks a definite approach to treatment options and duration. Therefore, combination therapies may be required especially in cases of serious organ involvement and disseminated disease [2-5]. Along with that, there are uncertainties as to the combination and duration of antibiotics effective against the microorganisms. In this report, a 12-year-old girl who was successfully treated with a combination therapy for hepatosplenic (HS) CSD was presented, and treatment methods in hepatosplenic CSD were briefly reviewed.

Ethics Statement

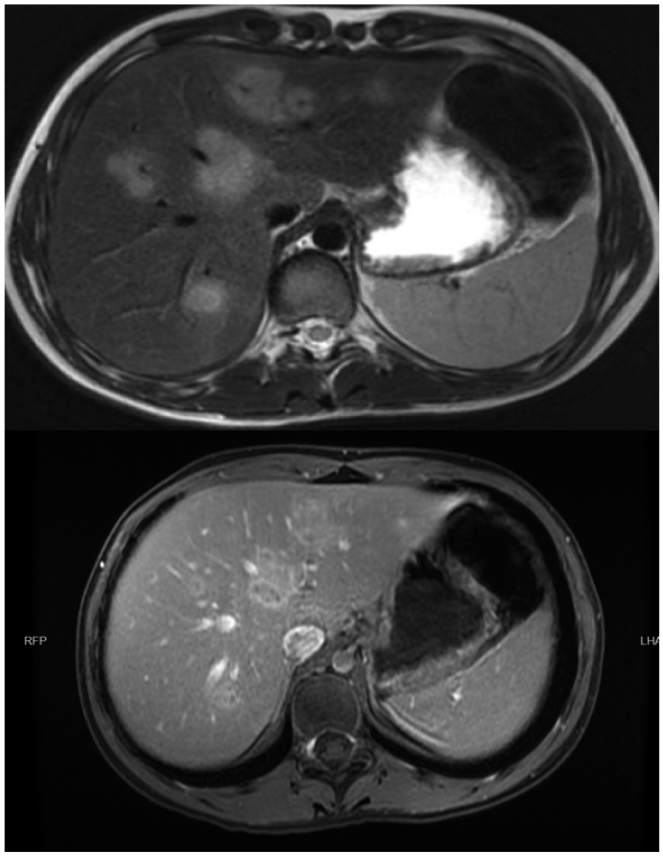
Written informed consent was obtained from the patient for publication of this case report and posted images.

Case Report

A previously healthy 12-year-old girl was admitted with complaints of axillary swelling and severe abdominal pain for the last one month. There was a history of feeding kittens for a few months at home and

the patient was often scratched by the cat. Oral clarithromycin treatment was initiated by the previous center considering CSD, but symptomatic improvement could not be achieved despite two weeks of treatment. Physical examination of the patient revealed no pathological findings other than 2×1 cm painless lymphadenopathy in the right axilla. Hemogram, peripheral blood smear and blood biochemistry were all normal. Acute phase reactants were markedly high, C-reactive protein was found as 3.4 (N: 0-0.8) mg/dL and erythrocyte sedimentation rate (ESR) was 115 (N: 0-20) mm/h. An axillary ultrasonography showed enlarged lymph nodes with cortex thickening, the largest one 19×11 mm diameter in the right axillary region. Abdominal ultrasonography revealed hepatomegaly with numerous hypoechoic lesions and contained millimetric anechoic cystic areas in the liver and spleen. Multiple heterogeneous contrast-enhancing lesions on liver and spleen, and periportal-paracaval enlarged lymph nodes were detected through magnetic resonance imaging (Figure 1). *Bartonella henselae* indirect immunofluorescence assay (IFA) IgG (Euroimmun, Lübeck, Germany) result was positive at 1/2048 titre, IgM was not analyzed as it was not included in the reference laboratory diagnostic kit. Additional organ involvement was not detected. A combination therapy with doxycycline and rifampicin for hepatosplenic CSD was initiated. After high fever and worsening of abdominal pain on the 7th day of treatment, hepatic biopsy and bone marrow aspiration were studied for differential diagnosis of possible diseases. Suppurative granulomatous hepatitis and micro-abscess foci were detected in liver biopsy while bone marrow aspiration was compatible with bacterial infection. Tuberculosis, tularemia, brucellosis, listeriosis, fungal infections and immunodeficiencies were excluded by the tests conducted. Culture or polymerase chain reaction from the tissue for *Bartonella* spp could not be applied. Fever developed under combined antibiotics were considered as Jarisch-Herxheimer-like reaction and treatment was not revised. The patient's fever quickly disappeared but the abdominal pain persisted until the first month of the treatment. Rifampicin was discontinued after 4 weeks. The ESR value of the patient, who was monitored with monthly examinations under doxycycline, returned to normal at the end of the second month. Doxycycline treatment was discontinued at six months, when the findings on hepatosplenic images were close to normal. Meantime, *Bartonella henselae* IFA IgG titre decreased to 1/512 and fixed at this level until the end of the treatment. Any serious drug-related side effects were not observed during the treatment.

Figure 1. Multiple heterogeneous contrast-enhancing lesions with millimetric cystic areas on liver and spleen. The largest one is at the junction of segment 2-4 on the right lobe inferior of the liver, and 29×18 mm diameter.



Discussion

Other than localized lymphadenopathy, which is the most common clinical manifestation of CSD and is self-limiting by treatment-free follow-up, organ involvements may require treatment [1-3]. *Bartonella* species are susceptible to many antibiotics in vitro. However, due to the remarkable discordance between in vitro and in vivo activity of antibiotics, treatment options are restricted to specific antibiotics such as macrolides (azithromycin, clarithromycin, erythromycin), ciprofloxacin, doxycycline, rifampicin, and trimethoprim-sulfamethoxazole [5]. These in vivo effective antibiotics can be used as monotherapy or combination therapies. Although there are a few reports that aminoglycosides, especially gentamicin, and ripampicin are bactericidal, all effective antibiotics have bacteriostatic activity on bacteria [6,7]. Therefore, combination regimens and long-term treatments can be chosen to increase the effectiveness of the treatment in cases with serious organ involvements or disseminated disease.

Table 1. Agents frequently used in treatment, treatment regimens, treatment approaches and recommendations for HS-CSD.

Treatment option	Primary indication	Recommendations	Optimum duration for treatment	Additional gain or disadvantage	References
Monotherapy					
Azithromycin	-Uncomplicated CSD in immunocompetent patients, especially with lymphadenopathy -The only prospective double-blind placebo-controlled study was conducted with azithromycin in non-complicated CSD	-No weighted recommendation for HS-CSD similar to uncomplicated CSD -Clinical response with short-term azithromycin monotherapy in HS-CSD was quite good in some reports	Uncertain, short (5 days) or long term therapy in various reports	Penetrates into macrophages and neutrophils, may transport into areas of inflammation and infection, remained high within the phagocytes when drugs are released	[2,3,8,10,12,13,14]
Gentamicin/Amikacin	-May be preferred as an initial parenteral treatment before switching to oral therapy in patients with severe HS-CSD -Especially in immunocompetent patients	Frequently preferred in severe CSD	Uncertain	-Clinical response may be obtained in as short as 48 hours with gentamicin monotherapy -It should be kept in mind that *Bartonellae* residing within erythrocytes are protected from gentamicin*	[8,12,16,17,18]
Ciprofloxacin	No approval for use in children	-Appears to be used as a rescue agent in cases where patient is unresponsive to initial medical treatment, rather than a first-line treatment -usually in the combination regimen -Rarely for HS-CSD	Uncertain, 2 weeks in some reports	Care should be taken in terms of possible long-term side effects during use	[12,16,17,19]
Rifampicin	-Associated with favorable clinical responses alone or in combination in HS-CSD - In immunocompromised and immunocompetent patients	Trimethoprim-sulfamethoxazole or gentamicin could be added to rifampicin if clinical response is not noted after 3 or 4 days in HS-CSD	Uncertain, 2 or 4-6 weeks in some reports	More effective than other antibiotics in some reports	[5,10,12,20]
Trimethoprim-sulfamethoxazole	May be preferred in initial combination treatment for severe HS-CSD	Frequently preferred in the combination regimens	Uncertain, 2-4 weeks in some reports	- Second agent after azithromycin for uncomplicated CSD with documented efectiveness at follow-up in some reports -May be preferred to doxycycline in combination regimens in patients < 8 years of age	[12,21,22]
Combination regimens					
Doxycycline *plus* rifampicin	-Retinitis, central nervous system involvement and HS-CSD -In immunocompromised and immunocompetent patients	May be preferred in initial treatment or in recurrence	Uncertain, 2 or 4-6 weeks or 4-6 months in some reports	Care should be taken about age-related drug toxicities when using doxycycline	[2,5,8,10,12]
Rifampicin *plus* gentamycin	May be preferred as initial combination regimen in patients with severe HS-CSD	No weighted recommendation for HS-CSD, may preferred in initial treatment	Uncertain, 4-6 weeks in some reports	Gentamicin-associated treatment failure may occur in combination regimens due to the above mentioned explanation (*)	[8,12,15]
Corticosteroids	- Neuroretinitis - The experiences in HS-CSD patients with serious symptoms or with a long-lasting course were shared in the literature	Not currently recommended routinely for HS-CSD treatment	N/A	May be applied for inflammation suppression in patients with uncontrolled fever or persistent disease	[16,23]
Surgical approach	Not a primary treatment approach	Invasive procedures in HS-CSD are rarely applied except for tissue diagnosis or unresponsiveness to the medical treatment	N/A	May be applied in the treatment of complications or as a rescue therapy	[5,11,24]

When treatment alternatives are thought to be bacteriostatic, two different groups of antibiotics may eradicate the bacteria in different niches in the host. The duration of treatment is unclear, and there are case-based reports indicating more successful results with combination regimens [4,5,8].

The HS form of the disease has been reported in 2.3% of cases [1]. Although the disease is a well-documented clinical entity, the efficacy of therapy for patients with HS-CSD remains unclear [9]. It is difficult to determine whether a single therapeutic approach is superior or beneficial in patients with HS-CSD than in others. The variety of regimen applied in the reports and the inconsistency in duration of the therapy are making it difficult to interpret. Agents used in treatment, treatment regimens, treatment approaches and recommendations for HS-CSD are summarized in Table 1.

A combination therapy was chosen for our patient who was unresponsive to the macrolide antibiotic initiated at the previous center, and because she had severe and persistent complaints with continuing clinical and radiological findings. The reason for the selection of a combination with rifampicin and doxycycline was the evidence that rifampicin is more effective both in combination and in monotherapy. This combination regimen has been used in previous reports in patients unresponsive to treatment and a good response was obtained [8]. Surgical procedure was required in our patient only for the diagnostic liver biopsy with justification of differential diagnosis. A Jarisch-Herxheimer–like reaction in immunocompromised patients during CSD treatment after the first several doses of antibiotics has been defined before [10]. We observed a reaction in our patient similar to Jarisch–Herxheimer reaction shortly after initiating the treatment. The reaction spontaneously disappeared without the need of additional treatment following the exclusion of other causes. Contrary to the literature, our case was an immunocompetent patient, however reaction was accepted as a treatment-related "Jarisch-Herxheimer–like reaction" since other possible causes were excluded. For our case, treatment response monitoring was based on the course of symptoms and clinical signs, the level of acute phase reactants, radiological recovery, and side effects of the drug. Since the improvement in symptoms and acute phase reactants occurred later than expected, it was decided to extend the treatment period with doxycycline and it was arranged in a way that was parallel to the radiological improvement. There are marked differences in treatment duration in combination regimens. Treatments given for periods ranging from 2 weeks to 6 months are available in the literature (Table 1). The duration of treatment was determined according to the course of the patient's symptoms and the status of radiological findings.

The preference for monotherapy or combination regimen in HS-CSD is predominantly determined by the clinician, according to the severity of the patient's clinical findings [5,8]. When the preference is a combination regimen, different combinations of any two agents from two different groups can also be chosen according to the suitability of the patient, apart from the combination regimens outlined above. In addition, the difference in the clinical response to antibiotics observed in immunocompromised and immunocompetent patients should not be overlooked [4,5]. The disease is self-limiting and spontaneous resolution that can sometimes be seen even in the case of common disease in immunocompetent patients remain true [1-3]. Taken together, the questions such as 'Are immunocompetent patients really in need of medical treatment? If any, which medication and how long?' are still unresponsive. Therefore, the role and effectivity of antimicrobial therapy in CSD require further investigation.

Authors' Contributions

S. Kanık-Yüksek, B. Gülhan, S. Hürmüzlü, A. Özkaya-Parlakay, A. Güneş, AS. Oğuz-Erdoğan and H. Tezer jointly wrote the manuscript and approved the final version.

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