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Case Report

Non-typhoid salmonella septic arthritis in dual living liver transplant recipient: a case report

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Non-typhoid salmonellosis is an infectious disease caused by *Salmonella* species other than *Salmonella typhi*. Although the usual clinical course of non-typhoid salmonellosis is a benign self-limiting gastroenteritis, these bacteria are especially problematic in immunocompromised individuals, including patients with malignancies, human immunodeficiency virus, or diabetes, and those receiving corticosteroids or other immunotherapy agents. In addition to enteric symptoms, *Salmonella* species give rise to extra-intestinal complications, including self-limiting arthritis, which appears 1 to 3 weeks after the onset of infection and lasts from a few weeks to several months. In some patients, however, this arthritis spears to be chronic in nature. We describe herein a living-donor liver transplant recipient who experienced non-typhoid Salmonella-triggered arthritis in the left hip. The patient recovered uneventfully after 6-month-long antibiotics treatment. Clinicians involved in transplantation should be aware of the possibility that transplant recipients, like other immunocompromised individuals, are at risk of salmonellosis and therefore require careful clinical and microbiological evaluation, with the goals of prevention and early recognition of infection. **(Korean J Hepatobiliary Pancreat Surg 2014;18:29-32)**

Key Words: Non-typhoid *salmonella*; Septic arthritis; Liver transplantation

INTRODUCTION

*Salmonella*e are enteric pathogens and a leading cause of bacterial food borne illness. Non-typhoid salmonellosis is an infectious disease caused by *Salmonella* species other than *Salmonella typhi*. In most patients, the clinical course of non-typhoid salmonellosis consists of a benign self-limiting gastroenteritis. However, these bacteria are especially problematic in immunocompromised individuals, including patients with malignancy, human immunodeficiency virus, or diabetes, and those treated with corticosteroids or other immunotherapy agents. In addition to enteric symptoms, *Salmonella* species give rise extra-intestinal complications, which are associated with increased mortality rates and graft failure in transplant recipients.

Salmonella-triggered arthritis may appear 1 to 3 weeks after the onset of infection. This arthritis is frequently asymmetric and migratory and usually involves the large joints. In most patients, this arthritis is self-limiting and lasts a few weeks to several months, but in some patients the disease appears to be chronic in nature. We describe here a patient who experienced non-typhoid *Salmonella*-triggered arthritis in the left hip after undergoing dual living-donor liver transplantation.

CASE

A 47-year-old man underwent a dual living-donor liver transplantation, consisting of the right lobe from his wife and the left lobe from his brother, due to hepatitis B, liver cirrhosis and hepatocellular carcinoma in February 2010. Postoperatively, he was treated with tacrolimus (initially 0.025 mg/kg/day intravenous injection switched into 3.5 mg per oral administration (per os) twice a day) and methyl prednisolone (initially 50 mg intravenous injection, every 6 hours switched into 12 mg per os twice a day). The serum level of tacrolimus was adjusted to 14.6 ng/ml (normal range, 5-20 ng/ml) and his graft function was excellent. He discharged in stable condition of day 24

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with immunosuppressants (Tacrobel® 3.5 mg and methylon® 12 mg, twice a day), acyclovir (Zovirax® 200 mg, once a day) and trimethoprim-sulfamethoxazole (400 mg-80 mg, Septrin® 2 tablets, every other day) to prevent rejection and infection. One week after discharge, he presented at the emergency room with a high fever (39.1°C), watery diarrhea, severe pain and stiffness in the left hip for 4 days. Blood tests showed hemoglobin 11 g/dl, leukocyte count 4,400/mm^3, platelet count 71,000/mm^3 and normal liver function test but C-reactive protein (CRP) concentration was 4.39 mg/dl. Blood cultures yielded group D *Salmonella*, which was sensitive to ampicillin, cefixime, and ceftriaxone, and resistant to quinolone. The patient had no joint problems preoperatively. Bilateral hip joint magnetic resonance imaging (MRI) revealed pyomyositis involving the left iliopsoas and external obturator muscles with abscesses in the iliopsoas muscle as well as diffuse synovial enhancement with increased joint effusion in the left hip joint (Fig. 1). Subsequent culture of synovial fluid from the left hip joint revealed no bacterial growth. He was treated empirically with intravenous ceftriaxone 2 g per day and all immunosuppressive agents were stopped for 3 days. Over the next 10 days of intravenous antibiotic treatment, his diarrhea and fever resolved, but pain and limited range of movement of the left hip continued. Three weeks later, follow-up MRI showed that the abscesses in his muscles had decreased but myositis was still present. Diffuse synovial thickening had progressed but the amount of joint effusion had decreased in the left hip (Fig. 2A). He was maintained on intravenous antibiotics for an additional 3 weeks, following which he was switched from intravenous ceftriaxone to oral cefixime 400 mg per day and sulfamethoxazole-trimethoprim (400 mg/80 mg) 2 tablets per day. After 5 weeks of antibiotic treatment, his joint pain improved progressively and he discharged with a further antibiotic treatment plan for a total of 6 months. An additional MRI, performed after 6 months of antibiotic therapy, revealed myositis and arthritis were markedly improved (Fig. 2B). Six months following his infection, his left hip had clinically improved. He had no joint disability and his graft function has remained stable for 22 months after liver transplantation.

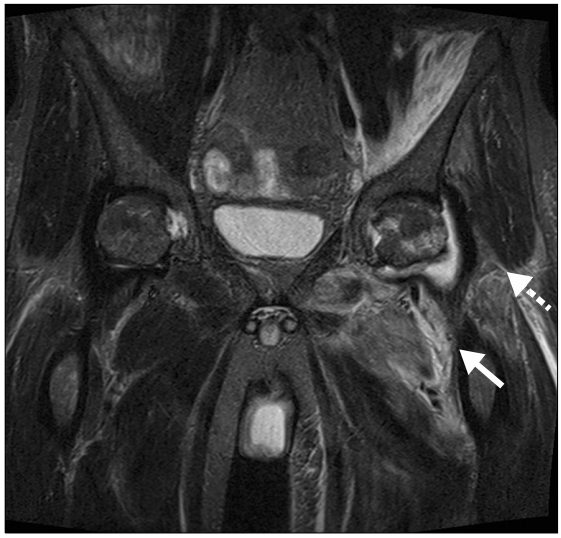

Fig. 1. Left hip MRI on admission, showing pyomyositis and an abscess in the iliopsoas muscle (arrow) and joint effusion (dotted arrow).

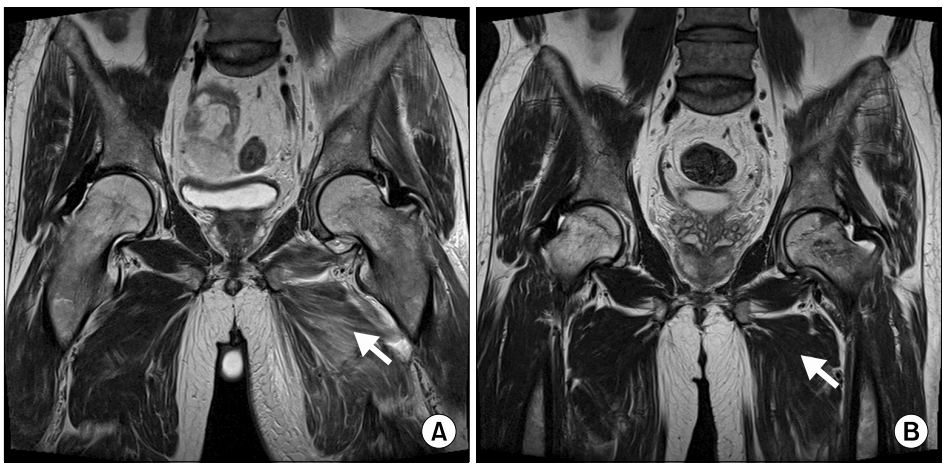

Fig. 2. (A) Left Hip MRI 3 weeks after admission, showing slightly improved myositis and decreased joint effusion (arrow). (B) Left hip MRI after 6 months of antibiotic treatment, showing markedly improved myositis and abscess (arrow).

DISCUSSION

To our knowledge, non-typhoid or typhoid *Salmonella*-triggered arthritis has not previously been reported in living-donor liver transplant recipients, although it has been described in several renal transplant recipients. *Salmonella* species are Gram-negative motile bacilli that are usually transmitted to susceptible hosts by consumption of contaminated foods, including beef, poultry, and eggs. Non-typhoid salmonellosis is an infectious disease caused by *Salmonella* species other than *Salmonella typhi*. Infection with non-typhoid *Salmonella* usually produces a self-limited gastroenteritis, but may also produce extra-intestinal complications, such as endocarditis, vascular infections, cholecystitis, hepatic and splenic abscesses, urinary tract infections, pneumonia or empyema, meningitis, septic arthritis, and osteomyelitis, all of which are associated with increased mortality rates and graft failure in transplant recipients.[1]

The severity of illness in individuals with salmonellosis is determined not only by the virulence of the infecting strain but also by host conditions. The most common risk factors include corticosteroid use, malignancy, diabetes, human immunodeficiency virus (HIV) infection, prior antimicrobial therapy and immunosuppressive therapy.[2] The rates of bacteremia and extra-intestinal complications are especially high in transplant recipients, approximately 60% and 35%, respectively.[3]

Among the extra-intestinal complications of salmonellosis is *Salmonella*-triggered arthritis, which may be septic or reactive. Reactive arthritis is defined as a new onset of swelling of a joint, inflammatory-type back pain, or extra-articular inflammation, occurring within 3 months of the onset of the gastrointestinal symptoms.[4] The pathogenesis of reactive arthritis remains obscure, although it is strongly associated with the presence of the major histocompatibility antigen HLA-B27, which may predict a more prolonged and severe disease.[5,6] The incidence of arthritis following *Salmonella* infections has been reported to range 2-15% and incidence of 3.4 % has been reported in renal transplant recipients.[1] The median times from onset of gastrointestinal symptoms to the development of arthritis have been found to range from 0 to 90 days, with the usual onset being within 7 to 14 days.[4-9]

The sequence of events that lead to bone and joint infection has not been well characterized and there are no antimicrobial guidelines for the identification of post-*Salmonella* arthritis. Ciprofloxacin has good *in vitro* activity against *Salmonella* owing to its high serum concentrations and intracellular penetration. However, the emergence of ciprofloxacin resistance and cross-resistance to unrelated antibiotics has been described in both immunocompetent and immunocompromised patients as our case. Although dual therapies with ciprofloxacin and chloramphenicol or trimethoprim have been used to reduce resistance, *Salmonella* strains resistant to multiple antibiotics have been isolated. Third-generation cephalosporins are active *in vitro* against *Salmonella* species, although the correlation between *in vitro* sensitivity and clinical response may vary due to differences in tissue and intracellular penetration. Ceftazidime has been replaced by ceftriaxone therapy due to its longer half-life, which has enabled once-daily treatment of outpatients.[10] Moreover, severe prolonged polyarticular reactive arthritis after intestinal salmonellosis is not altered by long-term antibiotic therapy. Appropriate physiotherapy, non-steroidal anti-inflammatory agents and local steroid injection have proven useful in the treatment of *Salmonella*-triggered arthritis. However, intra-articular injection of steroids is still considered problematic due to the possibility of secondary infections.[9,10] Clinical responses are based on the resolution of fever, pain and joint effusion.[11]

The prognosis of patients with arthritis after *Salmonella* infections has not been well defined. Although most patients show resolution of arthritis within 4 months of onset, chronic symptoms can persist for up to 5 years.[4] Moreover, relapse can occur, even with appropriate therapy. In an Israeli series, 2.2% of patients experienced a bacteriologically proven relapse.[12] The relapse rate is significantly higher in immunosuppressed patients, with recurrences occurring within a week to 2 years and 19 months after stopping antibiotics.1 It is difficult to adjust the level of immunosuppressants to prevent graft rejection while preserving immunocompetence against pathogens, especially during an active infectious stage. Total withdrawal of immunosuppressants has been reported successful in the treatment of refractory septic arthritis caused by *Salmonella* and *staphylococcus aureus*, together with preservation of graft function, in al long-term renal transplant recipient, although further long-term follow up study is

needed to delineate the effect of immunosuppressant withdrawal on renal allograft function.[9] In our patient, however, we withdrew immunosuppressive therapy for only 3 days to treat acute bacteremia, as complete withdrawal of such therapy was deemed dangerous for the patient. After resolution of his acute diarrhea and high fever, we resumed immunosuppressants and focused on eradication of ciprofloxacin-resistant *Salmonella* group D. Six months of antibiotic treatment have been recommended for HIV Patients with *Salmonella* bacteremia susceptible to ciprofloxacin.[13]

We herein report a dual living-donor liver transplant recipient who had quinolone-resistant, non-typhoidal samonella septic arthritis and that at least 6 months of treatment with cefixime and trimethoprim-sulfamethoxazole would lead to an acceptable outcome, as well as prevention of insidious progress of arthritis and permanent joint damage.

REFERENCES

1. Dhar JM, al-Khader AA, al-Sulaiman M, et al. Non-typhoid Salmonella in renal transplant recipients: a report of twenty cases and review of the literature. Q J Med 1991;78:235-250.
2. Hohmann EL. Nontyphoidal salmonellosis. Clin Infect Dis 2001; 2:263-269.
3. Kim AY, Glodberg MB, Rubin RH. Salmonella infections. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. Infectious diseases. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2004: 618-632.
4. Thomson GT, DeRubeis DA, Hodge MA, et al. Post-Salmonella reactive arthritis: late clinical sequelae in a point source cohort. Am J Med 1995;98:13-21.
5. Mäki-Ikola O, Granfors K. Salmonella-triggered reactive arthritis. Scand J Rheumatol 1992;21:265-270.
6. Thomson GT, Alfa M, Orr K, et al. Secretory immune response and clinical sequelae of Salmonella infection in a point source cohort. J Rheumatol 1994;21:132-137.
7. Chang JW, Tsai HL, Yang LY. Successful treatment of refractory septic arthritis caused by salmonella and staphylococcus aureus with preservation of graft function in a long-term renal transplant recipient by total withdrawal of immunosuppressants. Clin Nephrol 2010;73:72-75.
8. Inman RD, Johnston ME, Hodge M, et al. Postdysenteric reactive arthritis. A clinical and immunogenetic study following an outbreak of salmonellosis. Arthritis Rheum 1988;31:1377-1383.
9. Locht H, Kihlström E, Lindström FD. Reactive arthritis after Salmonella among medical doctors--study of an outbreak. J Rheumatol 1993;20:845-848.
10. Workman MR, Philpott-Howard J, Bragman S, et al. Emergence of ciprofloxacin resistance during treatment of Salmonella osteomyelitis in three patients with sickle cell disease. J Infect 1996; 32:27-32.
11. Habermann ET, Friedenthal RB. Septic arthritis associated with avascular necrosis of the femoral head. Clin Orthop Relat Res 1978;(134):325-331.
12. Meltzer E, Schwartz E. Enteric fever: an Israeli perspective. Isr Med Assoc J 2007;9:736-741.
13. Pegues DA, Miller SI. Salmonellosis. In: Fauci AS, Harrison TR, eds. Harrison's principles of internal medicine. 17 ed. New York: McGraw-Hill, 2008:956-961.