Salmonella septic arthritis in a patient with acute idiopathic thrombocytopenic purpura treated with steroid

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Salmonella has three clinical presentations: self-limiting gastroenteritis, a systemic syndrome (enteric or typhoid fever), and bacteremia with focal infection. Hematogenous infections can cause focal lesions, but unusual manifestations occur more often when predisposing factors such as T cell defect, hemolytic disorders (sickle cell disease, malaria) or trauma are present. Salmonella tend to invade bones and joints. There is no mention of acute idiopathic (immune) thrombocytopenic purpura as a predisposing factor for salmonella septic arthritis; however there are reports about the importance of platelets for the immune response. Here we present a case of Salmonella enteritidis septic arthritis following acute idiopathic (immune) thrombocytopenic purpura in a 15-year-old female patient who has been on steroid therapy for the last two weeks.

Key words: idiopathic thrombocytopenic purpura, septic arthritis, Salmonella enteritidis, steroid therapy.

Salmonellosis has three clinical presentations: self-limiting gastroenteritis, a systemic syndrome (enteric or typhoid fever), and bacteremia with focal infection. Asymptomatic intestinal and biliary existence of the microorganism (carrier state) is another clinical form. Focal lesion can involve unusual sites, presenting as meningitis; pleuropulmonary infection; endocarditis; pericarditis; arteritis; osteomyelitis; arthritis; splenic, hepatic, soft tissue and intra-abdominal abscess and urogenital disorders[1]. Hematogenous infections can cause focal lesions in eight percent of patients, but unusual manifestations more often occur when predisposing factors such as T cell defect, hemolytic disorders (sickle cell disease, malaria) or trauma are present[2]. Salmonella tends to invade bones and joints. Salmonella osteomyelitis and, more rarely, septic arthritis are seen, especially in patients with sickle cell anemia[3]. However, salmonella septic arthritis without any predisposing factor is also reported[4,5].

Here we present a case of Salmonella enteritidis septic arthritis following acute idiopathic (immune) thrombocytopenic purpura (ITP). To the best fo our knowledge this is the first salmonella septic arthritis case presented after ITP.

Case Report

A 15-year-old girl followed up by the Pediatric Hematology Department as acute ITP for the previous two weeks presented with right hip pain that limited her walking. Two weeks previously she had complained of sudden bruising and petechia but was in excellent health with an otherwise normal physical examination. Bone marrow aspiration revealed an increased number of megakaryocytes without leukemic cells. She had been treated with high-dose methylprednisolone (3 days 30 mg/kg, 3 days 20 mg/kg, and 4 days 10 mg/kg) as with our other ITP patient[6], but was accepted unresponsive. On the tenth day of therapy she was admitted to the emergency care unit with fever, right hip pain and scattered petechia.

Physical examination revealed tenderness, hyperemia, increased temperature and limited range of motion in the right hip joint, petechia predominantly on her legs and oral mucosa. There were no other remarkable

physical findings. Laboratory findings are given in Table I. Microscopic examination of stained blood film showed thrombocytopenia with leukocytosis, 68% being polymorphonuclear leukocytes with 100% toxic granulation and an erythrocyte sedimentation rate of 60 mm/hour. Emergency ultrasonography was reported as 12 mm effusion in the right hip joint. Hemarthrosis or septic arthritis was suspected; however, her thrombocytopenia prevented us from performing joint fluid aspiration to make differential diagnosis.

Table I. Laboratory Findings

Hemoglobin	: 12.9 g/dl (12-18)
Hematocrit	: 39%
WBC count	: 16,000/mm^3 (4,000-10,000/mm^3)
Platelet count	: 20,000/mm^3 (150,000-400,000/mm^3)
ESR	: 60 mm/h
Blood smear	: 68% PML, 10% lymphocyte, 20% monocyte, 2% eosinophil, toxic granulation 100%, rare and single platelet.
IgA	: 102 mg/dl (100-430 mg/dl)
IgM	: 110 mg/dl (80-400 mg/dl)
IgG	: 1160 mg/dl (800-1700 mg/dl)
C_3	: 123 mg/dl (90-180 mg/dl)
C_4	: 24 mg/dl (10-40 mg/dl)
Anti DNA	: Negative
ANA	: Negative
Anticardiolipin	IgM: Negative
	IgG: Negative
Anti CMV	IgM: Negative
	IgG: 250 IU/ml
Anti EBV	IgM: Negative
	IgG: Pozitive
Anti toxoplasma	IgM: Negative
	IgG: Pozitive
Anti HSV 1	IgM: Negative
	IgG: 1.281 IU/ml
Anti HSV 2	IgM: Negative
	IgG: 1.161 IU/ml
HB_sAg	: Negative
Anti-HB_s	: Negative
Anti-HB_C Total	: Negative
Anti HCV	: Negative
Stool culture	: Negative
Stool cultures (family)	: Negative
Salmonella agglutination	: O Ag group B: negative
	group D: 1/80
	H Ag group B: negative
	group D: negative
Salmonella agglutination (family)	: negative

WBC: white blood cell; ESR: erythrocyte sedimentation rate; PML: polymorphonuclear leukocytes; CMV: cytomegalovirus; EBV: Epstein-Barr virus.

The patient was hospitalized and cephalothin (100 mg/kg/day) and amikacin (15 mg/kg/day) were begun, assuming the patient was a septic arthritis case. Intravenous immunoglobulin (IVIG) treatment (400 mg/kg/day) was given for her thrombocytopenia. On the fifth day of this treatment, her platelet count reached 114,000/mm^3, and joint fulid aspiration was finally performed. Joint fluid was purulent; microscopic examination of Gram and Wright stained joint fluid revealed no microorganism but many polymorphonuclear leukocytes. Emergency exploration and debridement was performed. Purulent fluid in surgery and persistent fever led us to change her antibiotics to vancomycin (40 mg/kg) and amikacin (15 mg/kg). This combination was continued until Salmonella enteritidis was isolated from both blood and joint aspiration fluid culture bacterial susceptibility is given in Table II. In light of the antibiogram ciprofloxacin was started instead. Unfortunately her fever and pain did not subside, so to rule out endovascular complication of salmonella infection and echocardiographic examination was performed which showed normal echocardiographic findings. Sultamicilin was added to her treatment, and MRI of the hip joint revealed joint effusion and intramedullary edema in the femoral head, suggesting osteomyelitis. The joint was explored and the infected bone was debrided in a second operation.

Her clinical condition and laboratory parameters started to improve after the first and third week, respectively, and were normal within four weeks. She is now being followed after four weeks of antimicrobial therapy with a good clinical outcome.

Table II. Antibiotic Susceptibility
Salmonella Enteritidis

	Blood Culture	Joint Aspiration Fluid
Ciprofloxacin	Susceptible	Susceptible
Chloramphenicol	Resistant	Resistant
TMP/SMX*	Resistant	Resistant
Ampicillin	Resistant	Resistant
Amoxicillin/Clavulanic acid	Resistant	Resistant
Cefotaxime	Resistant	Resistant
Ceftriaxone	Resistant	Resistant

* Trimethoprim-sulfamethoxazole.

Discussion

Salmonella septic arthritis is a rare disease occurring in less than 0.3 percent of patients with nontyphoidal salmonellosis[7]. Sickle cell disease one of the well known presenting disorders in salmonella septic arthritis. Prior joint disease (rheumatoid arthritis, osteoarthritis, gout), previous trauma, connective tissue disease, lymphoma, hemolytic diseases and immunosuppressive treatment are

other common predisposing factors. Malnutrition is also accused in populations where salmonella is endemic[8]. Salmonella infection can cause two types of arthritis: monoarticular infectious arthritis and polyarticular subacute reactive arthritis[9]. The presence of bacterial lipopolysaccharides in the joint is a common and pathogenically important feature of reactive arthritis[10]. Circulating immune complexes activating both classical and alternative pathways are also effective in the pathogenesis of reactive arthritis[11].

Salmonella serotypes most commonly causing focal infections are S. hirschfeldii, S. cholerasuis and S. typhimurium. S. virchow has recently been reported as a cause of focal infection[12,13]. In our patient group D salmonella (S. typhi, S. enteritidis, S. gallinarum, S. ontario, S. II zuerich), Salmonella enteritidis (by serotyping study) was isolated from blood and joint aspiration fluid. Serotyping of salmonella species was performed by O somatic antigen, first phase H antigen and second phase antigen. In S. enteritidis, O somatic antigen was 9-12, first phase H antigen was Gm and second phase antigen was absent. In this way it was differentiated from other Group D salmonella. Similar to our case, S. enteritidis was reported in the literature to cause septic arthritis involving both knee joints in a 29-year-old man with Hodgkin's lymphoma[14].

There is no report of ITP as a predisposing factor for salmonella septic arthritis. In spite of this, there are reports about the importance of platelets for the immune response[15,16]. Platelets are known to 1. rapidly respond to sites of endovascular trauma and chemotactic stimuli associated with microbial colonization, and to be the earliest and predominant cells at sites of microbial colonization of vascular endothelium 2. possess surface receptors and cytoplasmic granules comparable in structure and function to neutrophils, monocytes and macrophages 3. adhere directly to and possibly internalize microbial pathogens, enhancing the clearance of these pathogens from the blood stream and limiting their potential for hematogenous dissemination 4. kill or damage bacterial, fungal, and protozoal pathogens in vitro 5. initiate or amplify complement fixation in the presence of microorganisms 6. release microbicidal proteins when stimulated in vitro with microorganisms or platelet agonists associated with infection 7. generate oxygen metabolites and 8. interact synergistically with leukocytes to exert enhanced antimicrobial functions in vitro[16]. Thus, thrombocytopenia increases the susceptibility to and severity of certain infections. Salmonella are in the group of microorganisms which are demonstrated to interact and aggregate with and be inhibited or killed by activated platelets in vitro[17-19]. Some reports implicate that salmonella resistant to platelet-derived microbicidal proteins in vivo may have increased virulence[20,21].

It is known that in systemic lupus erythematosus and hemolytic diseases impaired opsonization is relevant to the predisposition of salmonella septic arthritis[22]. Immune complexes are another common aspect of salmonella arthritis and ITP. ITP is an autoimmune disease in which immune complex formation may take place, and salmonella septic arthritis is associated with immune complexes. This leads one to think that although ITP and salmonella have complex outcomes they interacted some way in our patient.

Steroid therapy as immunosuppressive treatment is also known as a risk factor. The occurrence of salmonellosis may be related to the carrier state of the patient or to exposure to salmonella species. Sytemic lupus erythematosus (SLE) patients who are salmonella carriers are reported to develop septic arthritis when combined cyclophosphamide and prednisolone treatment is given[22]. Salmonella are microorganisms that live intracellularly; therefore, cellular immunity is the main host defense against salmonellosis. It is well known that impaired cellular immunity is a predisposing factor for salmonella septic arthritis. Corticosteroids cause alterations in leukocyte count (neutrophils increase, lymphocytes decrease), redistribution, suppression of migration to sites of inflammation, decreased response to mitogens, and decreased cytotoxicity[1]. Although complaints of our patient started early in steroid therapy, high-dose steroid may also have been a predisposing factor for infections in this patient.

It is concluded that in patients with ITP presented with septic arthritis, Salmonella should be suspected as an etiologic agent; both the disease itself and/or its treatment may predispose to the infections.

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