Recurrent *Salmonella enteritidis* sepsis and hepatic tuberculosis

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Abstract

A 33 year old woman with recurrent *Salmonella enteritidis* sepsis is described. Penicillins, ceftriaxone, ciprofloxacin, and chloramphenicol could not eradicate the salmonellas but a combination of high dose ciprofloxacin and ceftriaxone for the eighth episode successfully cured the infection. The combination of ciprofloxacin and ceftriaxone may be a valuable therapeutic regimen in patients with recurrent salmonella sepsis. Prolonged intrahepatic cholestasis resulting from granulomatous hepatitis in this patient improved considerably with empiric ursodeoxycholic acid treatment. A liver biopsy specimen showing non-caseating

epithelioid granulomas was positive for mycobacterial DNA by polymerase chain reaction. Repeated bronchoscopy with multiple biopsies eventually revealed caseating granulomas with acid fast bacilli in the lung biopsy specimens. Therefore, tuberculosis was diagnosed as the underlying disease and the cause of granulomatous hepatitis in this patient and tuberculostatic treatment was started. Polymerase chain reaction for mycobacterial DNA may be helpful in the differential diagnosis of hepatic granulomas when routine histological examination and culture of biopsy specimens are not diagnostic. Tuberculosis should be considered as one of the diseases predisposing to recurrent salmonella sepsis. (Gut 1995; 37: 136-139)

Keywords: *Salmonella enteritidis*, hepatic tuberculosis.

Figure 1: Histological examination of the patient's first liver biopsy specimen. (A) Two small epithelioid granulomas within the liver parenchyma; (B) larger epithelioid granuloma, note the absence of caseation necrosis. Haematoxylin and eosin, original magnification $\times 200$.

The incidence of non-typhoidal salmonella infections and septicaemias has increased during the past years resulting from the growing rate of food contamination by salmonellas and the increasing number of patients with immunosuppression.¹ Some recent important outbreaks were caused by *Salmonella enteritidis* and the frequency of *S enteritidis* isolates from blood cultures in patients with non-typhoidal salmonella septicaemia has risen sharply.² Standard antibiotic treatment can fail because of antibiotic resistance, impaired access of antibiotics to sites where salmonellas persist, or immune dysfunction in patients with underlying diseases.^{3 4} Relapsing salmonella sepsis in these patients raises important diagnostic and therapeutic problems.

We present a 33 year old woman with granulomatous hepatitis and *S enteritidis* septicaemia recurring eight times.

Case report

One year before presentation to our hospital a 33 year old white female nurse had been given tuberculostatic triple therapy (isoniazid, ethambutol, rifampin) because of a clinical suspicion of pulmonary tuberculosis (dry cough, subfebrile temperatures, miliar shadowing in the chest x ray, positive tuberculin skin testing); no granulomas or mycobacteria were found at bronchoscopy. Tuberculostatic therapy was stopped after three months for unknown reasons. Two months after the interruption of tuberculostatic treatment the patient had a short episode of febrile diarrhoea (negative stool cultures) followed by relapsing

TABLE I Antibiotic treatment of the salmonella septicaemias

Sepsis	Drugs, dose, and route	Duration (days)
1*	Piperacillin 4 g intravenously	2
	Ceftriaxone 1.5 g twice daily intravenously+gentamicin 160 mg intravenously	7
2*	Penicillin G 10 MU twice daily intravenously+gentamicin 240 mg intravenously	7
	Penicillin V 1.5 g thrice daily by mouth	7
3	Ciprofloxacin 200 mg twice daily intravenously	7
	Ciprofloxacin 250 mg twice daily by mouth	3†
4	Imipenem 1 g thrice daily intravenously+netilmicin 200 mg intravenously	6
	Ciprofloxacin 250 mg twice daily by mouth	10
5	Ciprofloxacin 200 mg twice daily intravenously	7
	Ciprofloxacin 250 mg twice daily by mouth	3†
6	Ciprofloxacin 200 mg twice daily intravenously	7
	Amoxycillin 2 g thrice daily by mouth	8
	Amoxycillin 750 mg thrice daily by mouth	28
7	Chloramphenicol total 20 g intravenously	14
8	Ciprofloxacin 200 mg four times daily intravenously+ceftriaxone 2 g twice daily intravenously	14

*Before presentation to our hospital; †discontinued by the patient.

fever attacks lasting three to four days every four to six weeks. Five months later septic fever and considerable abdominal tenderness led to exploratory laparotomy in another hospital. Intraoperative needle biopsy of the enlarged liver showed non-caseating epithelioid granulomas (Fig 1). Staining for acid fast bacilli was negative. Four days after discharge the patient had another septic episode, which again resolved quickly with intravenous antibiotics (Table I).

Four weeks later she developed her third episode of septic temperatures of up to 41°C and was transferred to our hospital in July 1992. Blood cultures were positive for *S. enteritidis* (antigen formula: 1, 9, 12: g, m; phage typing: RDNC). The isolate was susceptible to penicillins, cephalosporins, tetracyclines, sulphonamides, quinolones, aminoglycosides, and chloramphenicol. Stool and urine cultures were negative. The total leucocyte count was 5100/μl with relative neutrophilia (4% bands, 74% segmented) and toxic granulation. The aspartate aminotransferase was 29 IU/l (normal 0–18), alanine aminotransferase 52 IU/l (0–22), γ-glutamyltransferase 371 IU/l (6–28), alkaline phosphatase 2788 IU/l (60–170), leucine aminopeptidase 240 U/l (11–35), and angiotensin converting enzyme 82 IU/l (18–55). The Gruber-Widal reaction and specific serum antibodies to salmonellas were positive.⁵ Chest x ray showed minimal lymph node calcifications. Abdominal ultrasound and computed tomography of the abdomen showed hepatosplenomegaly. The fever resolved within 24 hours with intravenous ciprofloxacin (Table I).

The patient was readmitted to our hospital with additional septic episodes one, six, seven, 10, and 11 months after presentation. Blood cultures were positive for *S. enteritidis* of the same antigen formula and phage type each time. Stool culture during the fourth episode

and duodenal bile aspiration before antibiotic treatment of the eighth episode were positive for the same *S. enteritidis*. All other cultures of stool, duodenal aspirates, and urine were negative. The fever resolved quickly with antibiotic therapy at each septic episode (Table I). The eighth episode was treated with high dose intravenous ciprofloxacin (200 mg four times daily) and ceftriaxone (2 g twice daily) for 14 days (Table II). This regimen successfully prevented further septicaemias.

An extensive search for underlying disorders was carried out after the third salmonella episode. High resolution computed tomography of the chest showed minimal subpleural thickening in the posterior segment of the right upper lobe. Gallium scintigraphy showed [⁶⁷Ga]citrate uptake in liver and spleen, both lacrimal glands (panda sign) and intrathoracic hilar lymph nodes (lambda sign). Two bronchoscopies with transbronchial biopsy specimens showed chronic interstitial pneumonia without granulomas and a normal CD4/CD8 ratio in the bronchoalveolar lavage. The gallium scintigraphy findings, increased serum angiotensin converting enzyme concentrations and granulomatous hepatitis first led us to suspect sarcoidosis as the underlying disease. The patient was given a 10 week course of oral prednisolone. Serum alkaline phosphatase concentrations began to fall even before prednisolone was begun and started to rise during treatment (Fig 2). Repeat liver biopsy showed non-specific reactive hepatitis and mild steatosis without granulomas. Endoscopic retrograde cholangiography, oral cholecystography, intravenous urography, bone scan, and echocardiography were normal. Liver function tests remained raised after the last salmonella episode and ultrasound showed persistent hepatosplenomegaly. The patient was given empirically ursodeoxycholic acid (UDCA; 10 mg/kg body weight) and serum alkaline phosphatase dropped considerably (Fig 2).

Fluorescence activated cell sorting analysis of peripheral white blood cells performed five days before the sixth and ninth months after the last salmonella episode showed increased T suppressor and normal T helper cells (CD4/CD8 ratio 0.32 and 0.46, respectively). Antibody testing and polymerase chain reaction in the serum were negative for HIV. Skin testing was positive for tuberculosis and tetanus. Phagocytosis capacity and oxidative burst in macrophages and granulocytes were normal.

Six months after the last salmonella episode fever up to 38.5°C recurred. The patient had lost 12 kg within six weeks. All routine bacteriological cultures including multiple stool cultures for *S. enteritidis* remained negative. Chest x ray showed a subsegmental infiltrate in the posterior left lower lobe that persisted for two weeks with intravenous doxycycline followed by imipenem. Repeated bronchoscopy with multiple biopsies eventually showed epithelioid cell granulomas with central caseating necrosis and acid fast bacilli. When the polymerase chain reaction method⁶ became available both liver biopsy specimens

TABLE II Antibiotic treatment of the eighth episode

	Time (h)					
	6	9	12	15	18	21
Ciprofloxacin	200 mg		200 mg		200 mg	200 mg
Ceftriaxone		2 g				2 g

Figure 2: Clinical profile of the patient. Eight arrows indicate the eight *S. enteritidis* septicaemias, LBx=liver biopsy. GGT= γ -glutamyltransferase, alk phos=alkaline phosphatase. Bars indicate the medical treatment: Predn=prednisolone, UDCA=ursodeoxycholic acid, Tb=tuberculostatic therapy (isoniazid, rifampicin, pyrazinamide for eight weeks, followed by isoniazid and ethambutol).

were positive for mycobacterial DNA (Fig 3). The fever and pulmonary infiltrate resolved quickly with tuberculostatic therapy (isoniazid, rifampin, pyrazinamide). Serum angiotensin converting enzyme concentrations became normal and the liver function tests continued to improve (Fig 2). More than one year after the last *S. enteritidis* episode the patient is asymptomatic and in a good clinical condition.

Discussion

We report a case of *S. enteritidis* sepsis relapsing eight times within one year. Underlying disorders favouring salmonella septicaemia that had to be ruled out in our patient were

Figure 3: Polymerase chain reaction (PCR) for mycobacterial DNA in the patient's liver biopsy specimens. Amplification of mycobacterial DNA by PCR (3% agarose gel) was carried out using primers that amplify a 143 bp long fragment (arrow) of the gene for the 65 kD membrane antigen. Both liver biopsy specimens were positive for mycobacterial DNA. Lanes: 1=molecular weight marker, 2=first liver biopsy, 3=second liver biopsy, 4=negative control (normal liver tissue, necropsy material), 5=positive control (tuberculosis of the lung, biopsy specimen). The second DNA bands at the top of lanes 2–4 represent non-specific high molecular weight DNA (larger than 20 kD).

haemolytic conditions,³ histoplasmosis,⁷ schistosomiasis,⁸ neoplasias,⁹ collagenosis,¹⁰ sarcoidosis, and AIDS.⁴ Particularly in AIDS, relapsing episodes of septicaemia may occur.⁴ Immunosuppressive therapy, longterm haemodialysis, and splenectomy are further important conditions predisposing to recurrent salmonella sepsis.¹¹ Fluorescence activated cell sorting analysis of peripheral white blood cells showed increased T suppressor cells with a reduced CD4/CD8 ratio; such findings have been reported in patients with prolonged salmonella and mycobacterial infections.^{12,13}

An intensive search for chronic salmonella carriage in the gastrointestinal and urinary tract was negative in our patient. The presence of *S. enteritidis* in duodenal aspirate during the last episode was considered a secondary phenomenon because salmonellas may have entered the biliary tract from blood during septicaemia.¹⁴ Persistence of *S. enteritidis* in the reticuloendothelial system could explain recurrent endogenous septicaemias in our patient.¹⁵

There are no therapeutic standards for patients with recurrent salmonella sepsis. The antibiotic treatment regimens for the patient's first to seventh septicaemia including penicillins, ceftriaxone, ciprofloxacin, and chloramphenicol were not successful in preventing relapsing sepsis (Table I). These antibiotics were highly effective against *S. enteritidis* in vitro, but they may have failed in vivo because of limited concentrations in intracellular compartments where salmonellas can persist.³ Recent data suggest that quinolones or third generation cephalosporins are more effective in the treatment of salmonella infections than penicillins, cotrimoxazole, or chloramphenicol.^{11,16} Although both ciprofloxacin and ceftriaxone show excellent intracellular activity,¹⁶ standard doses of ciprofloxacin (200 mg twice daily intravenously or 250 mg twice daily by mouth) or ceftriaxone (2 g intravenously per day) seem to be inadequate in treating patients with recurrent salmonella sepsis. Combined high dose ciprofloxacin (200 mg four times daily intravenously) and ceftriaxone (2 g twice daily intravenously) for 14 days (Table II) was finally successful in eradicating the salmonellas in our patient. Eradication by a combination of ciprofloxacin and ceftriaxone has been reported in an immunodeficient 8 year old boy with relapsing *S. dublin* septicaemia.¹⁷ The combination of ciprofloxacin and ceftriaxone may be a valuable therapeutic regimen in patients with recurrent salmonella sepsis. High dose oral ciprofloxacin (750 mg twice daily) and intravenous ciprofloxacin (200 mg four times daily)¹⁸ have similar pharmacokinetics and are of comparable therapeutic efficacy.¹⁹

The liver function tests with considerably raised serum alkaline phosphatase concentrations were caused by granulomatous hepatitis (Figs 1 and 2).²⁰ The differential diagnosis of hepatic granulomas includes an extensive list of infectious and non-infectious conditions.^{21,22} Positive lambda and panda signs at gallium scintigraphy and increased serum angiotensin

converting enzyme concentrations initially led us to suspect sarcoidosis.²³ Another explanation for granulomatous hepatitis considered in our patient was continued infection with *S. enteritidis*. In typhoid fever histologically non-specific reactive hepatitis is common,²⁴ whereas granulomatous hepatitis is rare.²⁵ Non-typhoidal salmonellas have been shown to induce liver granulomas in mice under experimental conditions.²⁶ However, Gram staining could not show rods within liver granulomas in our patient. We decided to start an empiric course of UDCA (Fig 2) because it is effective in the treatment of a wide variety of cholestatic conditions and has no serious side effects.²⁷

Repeated bronchoscopy with multiple biopsies finally showed caseating granulomas and acid fast bacilli thus pointing to tuberculosis as the underlying disease and the most probable cause of liver granulomas in this patient.²⁸ A positive polymerase chain reaction for mycobacterial DNA obtained from both liver biopsies further supported the diagnosis of hepatic tuberculosis. The histopathological patterns of tuberculous liver granulomas vary widely.²⁹ As caseation necrosis may be absent and stains for acid fast bacilli are usually negative,²¹ the diagnosis of hepatic tuberculosis needs a high index of clinical suspicion.³⁰ Fever of unknown origin, positive tuberculin skin testing, anaemia, and weight loss clinically suggest tuberculosis rather than other causes of hepatic granulomas.²¹ Polymerase chain reaction for mycobacterial DNA may be helpful in the differential diagnosis of hepatic granulomas when routine histological tests and cultures of biopsy specimens are not diagnostic. Mycobacterial DNA, however, has also been detected in some cases of pulmonary sarcoidosis.⁶

Tuberculosis itself may impair cell mediated immunity,³¹ thus explaining our patient's susceptibility to recurrent *S. enteritidis* septicaemia. Infection of macrophages by mycobacteria might interfere with their ability to kill other intracellular pathogens such as salmonellas.⁷ Because mycobacteria are susceptible to quinolones,³² repeated ciprofloxacin treatment of salmonellosis may have masked tuberculosis, thus delaying the diagnosis of the underlying disease in our patient.

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