SciMedCentral

JSM Gastroenterology and Hepatology

Case Report

Salmonellosis in a Patient on Natalizumab for Ulcerative Colitis and Multiple Sclerosis

Adam Faye[1], Yasmin Metz[2], Barry Hartman[3], Carl V. Crawford[2]* and Ellen Scherl[2]

[1]*Department of Medicine, Columbia University Medical Center, USA*
[2]*Division of Gastroenterology, Weill Cornell Medical College, USA*
[3]*Division of Infectious Diseases, Weill Cornell Medical College, USA*

***Corresponding author**
Carl V. Crawford, 2Division of Gastroenterology, Weill Cornell Medical College, 1305 York Avenue 4th Floor, NY, NY 10021, USA, Tel: 646-962-4000; Fax: 646-962-0110; Email: cvc9002@med.cornell.edu

Submitted: 04 August 2015

Accepted: 13 January 2016

Published: 14 January 2016

Keywords

- Salmonella
- Natalizumab
- Selective adhesion molecule
- Ulcerative colitis

Abstract

Salmonella enterica is a gram negative enteric pathogen that is acquired via oral ingestion of contaminated food or water. Diarrheal disease caused by non-typhoidal *Salmonella serovars* (NTS) such as *Salmonella enteritidis* results in a colitis that mimics ulcerative colitis (UC). While NTS in immune competent adults is typically self-limiting, NTS in those who are immune suppressed can increase the risk of bacteremia and mortality and requires treatment with antibiotics. The use of biologic therapy in patients with inflammatory bowel disease can lead to relapsing *Salmonella* infection. However, to our knowledge there are no reports of patients who develop *Salmonella* infection while on selective adhesion molecule (SAM) inhibitor class therapy. A 49-year-old woman with well-controlled left sided UC and an 11-year diagnosis of multiple sclerosis (MS) presented with new onset abdominal cramping, non-bloody diarrhea, rash, and pain in her joints with stool studies positive for *Salmonella enteritidis*. The patient was treated with antibiotics but had recurring symptoms and multiple positive stool cultures requiring temporary discontinuation of natalizumab (NTZ) and an extended course of rifaximin. NTZ is a recombinant humanized IgG4 monoclonal antibody that blocks α4 integrin, a lymphocyte adhesion molecule. It prevents chemotaxis of inflammatory cells from the bloodstream into inflamed tissues, and thus reduces the host's ability to clear salmonella. We report the first case of a relapsing NTS infection in a patient on SAM therapy, suggesting that this therapy significantly impairs the function of the innate immune system against *Salmonella* infections.

ABBREVIATIONS

NTS: Non-Typhoidal Salmonella; NTZ: Natalizumab; IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease; RA: Rheumatoid Arthritis; SAM: Selective Adhesion Molecule; MS: Multiple Sclerosis; ESR: Erythrocyte Sedimentation Rate

INTRODUCTION

Salmonella enterica (*S. enterica*) is a gram-negative enteric pathogen that is acquired via oral ingestion of contaminated food or water and may clinically manifest as enterocolitis, bacteremia, and/or systemic disease. *Salmonella* infects humans by adherence to gut epithelium and translocation across the gut barrier by bacterial-mediated endocytosis. Upon contact with enterocytes, the bacterium uses its T3SS (SPI1) complex to allow for translocation of effector molecules into the host cell cytoplasm. This results in cytoskeletal rearrangement and upregulation of pro-inflammatory cytokines including IL-8, which promotes neutrophil migration (Figure 1). Consequently, intracellular uptake of the bacterium, disruption of tight junctions, and chemotaxis of the innate immune system leads to gut inflammation and subsequent diarrhea [1].

The specific manifestations of illness depend upon the serovar of *S. enterica* as well as the immune status of the host. *Salmonella enteriditis* (*S. enteriditis*) is a non-typhoidal *Salmonella* (NTS) that causes a colitis similar to that of ulcerative colitis (UC), whereas *Salmonella* Typhi and *Salmonella* Paratyphi cause typhoid fever and small bowel enteritis respectively. The importance of understanding these infections and identifying those at risk are evidenced by the 1.3 billion cases each year and thousands of resulting deaths [2].

Immunosuppression can increase the likelihood of infection with *Salmonella.* This increased risk specifically correlates with the NTS serovar and presents with a more severe and invasive disease in immunocompromised hosts than in those who are immunocompetent [3,4]. In rare instances brain abscesses

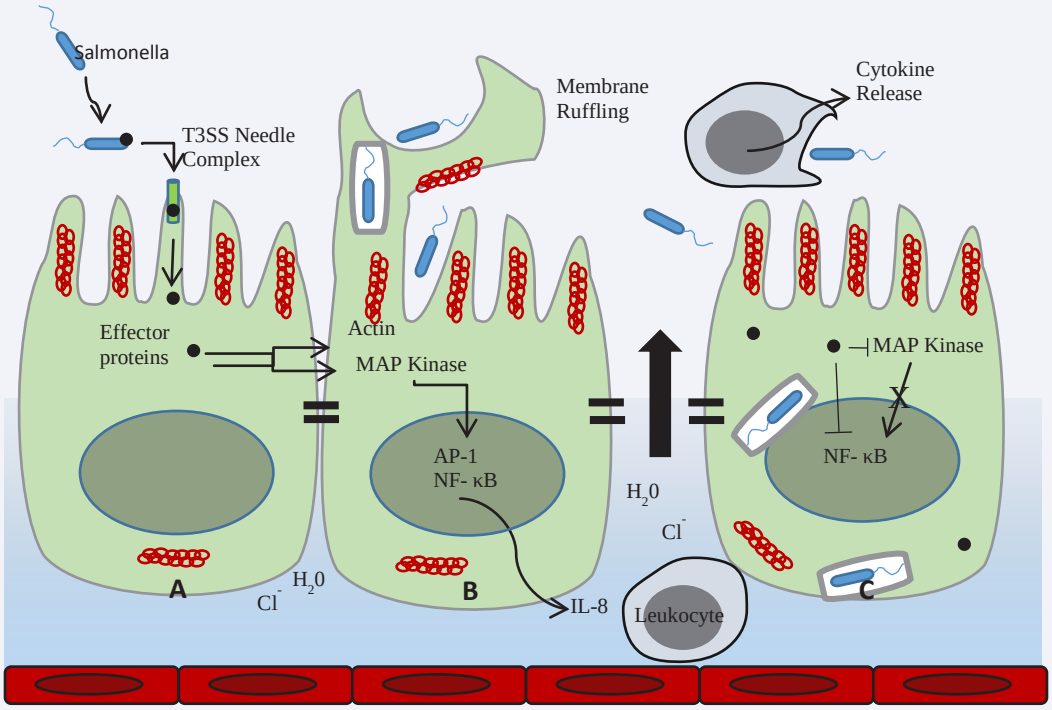

Figure 1 *Salmonella* releases effector proteins into enterocytes (A) that then interact with the cell to induce membrane ruffling, disruption of tight junctions, release of pro-inflammatory cytokines (B), and ultimately reversal of these effects (C).

have been reported from *Salmonella* infections, specifically in immunocompromised patients [5]. Other individuals at risk for infection with NTS include young children, elderly patients, patients with achlorhydria, atrophic gastritis or previous gastric surgery [6,7], patients on acid-suppressing medications [8], and patients reporting recent antibiotic use [9]. Interestingly, immunocompromised individuals do not appear to be at increased risk for typhoid fever, although the *Salmonella* Typhi serovar is an invasive and systemic pathogen [3].

The use of chimeric or humanized anti-TNF therapy in patients with inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) also confers an immunocompromised status. In mouse models it has been shown that anti-TNF therapy can enhance *Salmonella* infection and increase likelihood of relapse [10]. There are several case reports of invasive NTS disease in patients with RA treated with anti-TNF, but there are no reports of patients who develop recurring *Salmonella* infection while on a selective adhesion molecule (SAM) inhibitor class therapy.

CASE PRESENTATION

A 49-year-old woman with well-controlled left-sided UC over the last two decades and an 11-year diagnosis of multiple sclerosis (MS) presented for follow up at the Weill Cornell Medical College-Roberts Center for Inflammatory Bowel Disease. She reported an acute change in her quiescent disease with complaints of severe, intermittent, generalized abdominal pain with cramping. One week after the onset of abdominal pain, the patient developed 7-8 non-bloody episodes of watery diarrhea daily. The patient also reported new-onset rose-colored papules on her chest and flank and large joint arthralgias and pains in her wrist, hips, and elbows with no associated swelling. Her medications consisted of natalizumab 300mg IV and methylprednisolone 250 mg IV monthly for the last 3 years and balsalazide 6.75g daily. The patient was afebrile with a benign physical exam. Her abdomen was without distention, tenderness, rebound, guarding or a Murphy's sign, and her skin was remarkable for six rose colored papules on the chest and flank. Laboratory data was significant for a slightly elevated creatinine of 1.1 mg/dL, a leukocytosis of 11,200 cells/uL, and erythrocyte sedimentation rate (ESR) of 30 mm/hr. Stool studies showed elevated calprotectin and negative *Clostridium difficile* toxin with cultures positive for *S. enteritidis.* Flexible sigmoidoscopy showed mild proctitis with no evidence of acute exacerbation of UC on biopsy.

One week following the positive stool culture, the patient's diarrhea persisted despite slight improvement, and she was started on a 10 day course of ciprofloxacin 500mg BID. Natalizumab and methylprednisolone treatments were stopped.

The patient only completed a three-day course of ciprofloxacin due to tendinitis in her ankle and calf. She subsequently was started on a three-day course of rifaximin 200mg TID. Of note, the *Salmonella enteriditis* was tested for sensitivity to the following antibiotics (with resultant sensitivities; breakpoints; susceptibilities): Ampicillin (MIC ≤ 2 μg/mL; Breakpoint ≤ 8 μg/mL; Susceptible), Ceftriaxone (MIC ≤ 1 μg/mL; Breakpoint ≤ 1 μg/mL; Susceptible), Levofloxacin (MIC ≤ 0.12 μg/mL; Breakpoint ≤ 2 μg/mL; Susceptible), Trimethoprim/Sulfamethoxazole (MIC ≤ 20 μg/mL; Breakpoint ≤ 38 μg/mL; Susceptible). Although susceptibility to rifaximin was not tested, it was used since the patient had allergies to ampicillin and sulfa drugs and was unable to tolerate fluoroquinolones.

One week after finishing the three-day course of rifaximin

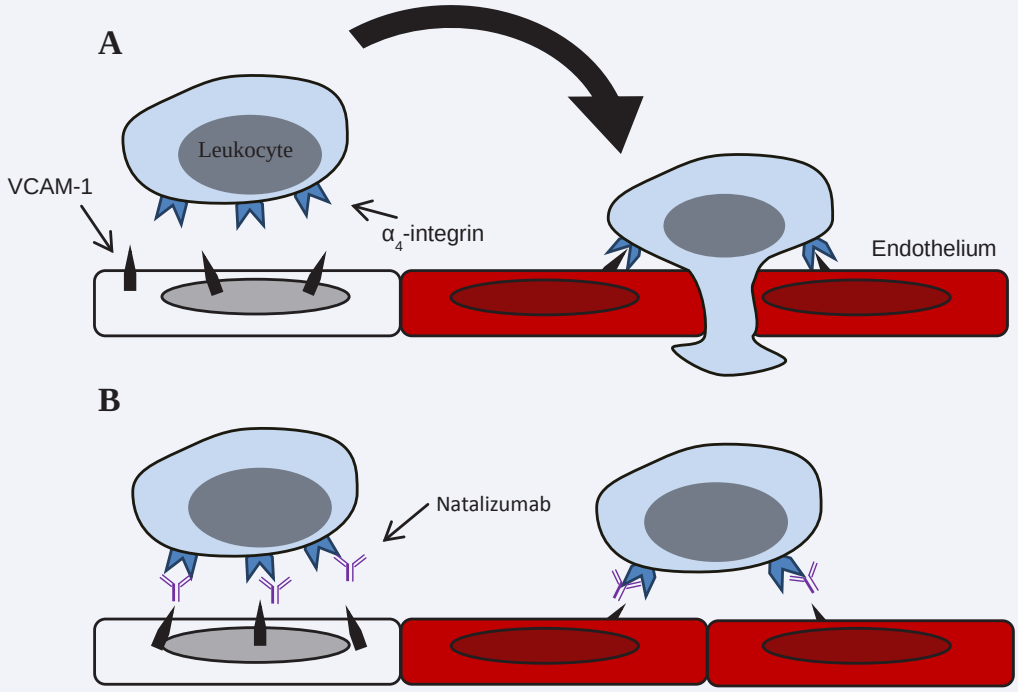

Figure 2 Transmigration of leukocyte across endothelium (A). Natalizumab binding α_4-integrin and blocking adhesion to VCAM on endothelium, thus inhibiting diapedesis (B).

the patient reported recurring abdominal pains and cramps, and she was restarted on rifaximin 200mg TID for 10 days. Her stool culture returned negative at the time, although it was positive again for *Salmonella enteriditis* three weeks later with the patient reporting persistent abdominal discomfort, hip pain, and diarrhea. She was given another course of rifaximin for 10 days.

Four weeks later, a third follow-up stool culture was obtained that was again positive for *Salmonella enteriditis*, and had the same phenotype (MIC values and susceptibilities) as the original *Salmonella* species, suggesting a relapse of the original infection. Rifaximin 600mg BID was initiated for an extended duration of three months. She had a negative stool culture one month into her prolonged treatment course with resolution of symptoms, and had persistently negative cultures for the next several months. Her immunosuppressive therapy comprising of natalizumab and methyl prednisolone were subsequently restarted.

DISCUSSION

To understand the progression of this patient's disease, it is helpful to examine the relationship between *Salmonella* infections and Inflammatory Bowel Disease (IBD, comprising UC and CD). Both genetic predisposition and environmental factors are thought to contribute to IBD, and it is hypothesized that in this family of diseases, dysregulated immune responses directed against normal luminal bacteria and their products result in chronic inflammation [11]. However, a few population-based studies have actually suggested that enteric infections caused by pathogens such as *Salmonella* and *Campylobacter* may lead to the development of IBD. These studies showed an increased risk of IBD following an episode of infectious gastroenteritis, particularly in the first year of follow up [12,13]. Jess *et al.*, however, also measured the incidence rate ratio for IBD in those with negative stool studies and noted a similar risk pattern, which supports the hypothesis that the observed increase in occurrence of acute bacterial gastroenteritis prior to the diagnosis of IBD may actually reflect a detection bias secondary to repeated stool testing [14].

Although a direct link between *Salmonella* infection and IBD may not be present, case reports and mouse models have shown that patients with IBD and/or RA who are on immunosuppressive therapy are at increased risk for severe and systemic disease when infected with NTS [3,15]. In immunocompetent adults, diarrheal disease caused by NTS is typically self-limiting, and antibiotic treatment does not improve clinical outcome [16]. In patients that are immunosuppressed, however, data show a higher incidence of NTS bacteremia and an overall increase in total mortality; guidelines thus endorse usage of antibiotics in this population of patients [3]. Typically, immunosuppressed patients infected with NTS present primarily with *Salmonella* bacteremia, absent of diarrheal disease [3,4]. Although our patient presented predominantly with diarrhea (it is unknown if she was also bacteremic as blood cultures were not obtained), antibiotics were prescribed due to her immunocompromised state on both methylprednisolone and natalizumab, a recombinant humanized IgG4 monoclonal antibody directed against α4 integrins.

Fluoroquinolones are usually first-line therapy for *Salmonella* infections due to their intracellular activity, but broad-spectrum antibiotics such as ampicillin and non-absorbable drugs such as neomycin have also been used [16]. Notably, rifaximin has not been proven as an efficacious therapy against *Salmonella*, but small scale studies have shown resolution of symptoms after its use [17]. This, in conjunction with the patient's allergies and

development of tendonitis while on fluoroquinolones, justified our use of rifaximin.

Natalizumab is FDA approved for the treatment of MS and as a second line biologic for the treatment of CD in patients who have failed anti-TNF therapy. It is highly effective; a dose of 300mg IV once a month induces remission in ~45% of adults with IBD (specifically those with elevated c-reactive protein, active disease despite immunosuppressants, or prior anti-TNF therapy) as compared to ~25% remission in the placebo group [18]. Its drawback is a potential risk (1:1,000) of progressive multifocal leukoencephalopathy caused by the human polyomavirus JC virus, which is often irreversible [19]. Natalizumab is generally well tolerated, but it is also associated with an increased risk for infections (specifically influenza), acute hypersensitivity reactions, and hepatotoxicity.

Natalizumab acts by binding to the α4 subunit of α4β1 (very late antigen-4 [VLA-4]) and α4β7 integrins that are expressed on macrophages and lymphocytes. This action effectively inhibits the interaction between VLA-4 and its receptor, vascular endothelial adhesion molecule-1 (VCAM-1), resulting in disruption of leukocyte chemotaxis across the vascular endothelium (Figure 2) [20]. Chemotaxis is a necessary event for efficient migration of leukocytes across the endothelium and its blockade reduces the recruitment of immune cells into sites of inflammation. By inhibiting macrophage and lymphocyte migration, natalizumab impedes local cytokine release of TGFß1, IL-12, IL-18 and IL-23, which are responsible for the upregulation of IFN-γ release from T_H1 lymphocytes. This limits the host's ability to mount an effective cell-mediated immune response necessary to eliminate the *Salmonella* infection. Notably, neutrophil chemotaxis is not directly inhibited with the use of natalizumab, as neutrophils have a different set of cell adhesion molecules, CD11b/CD18. However, natalizumab may indirectly inhibit neutrophil migration by preventing interactions between leukocytes and the extracellular matrix proteins fibronectin and osteopontin. These interactions have been implicated in the release of proinflammatory cytokines (such as IL-8) which are responsible for neutrophil chemotaxis [21, 22]. This further inhibits the host's innate immune response, and we therefore favor treating any manifestation of symptomatic NTS in patients on natalizumab with antibiotics.

In addition, this case suggests that immunosuppressed individuals on methylprednisolone and natalizumab may require a longer duration of therapy than may be required with immunocompetent patients. Although both medications suppress the immune system, we suspect natalizumab to be the primary cause for the patients' continued symptoms and positive stool cultures given that IV methylprednisolone is highly soluble with a short half-life and was immediately stopped early within the patient's course. The elimination half-life of natalizumab is approximately one week, with receptor saturation remaining for one, three to four, and six weeks depending upon dose (1, 3, and 6 mg/kg respectively) [21]. Our patient's dose of 4 mg/kg equates to a receptor saturation time of approximately four to five weeks, and our patient reported permanent resolution of symptoms only after a prolonged treatment course with antibiotics. We believe that the recurrence of NTS in our patient was due to relapse, given that on repeated stool cultures, the Salmonella were of the same serovar and had identical phenotypes. Unfortunately, neither phagetyping nor molecular analysis was performed on either isolate to definitively determine that the same strain caused these infections.

In summary, NTS can cause life-threatening infections in immunocompromised individuals, including those with IBD on immunotherapy. An intact mucosal barrier and the preservation of antimicrobial processes play a major role in the infectivity of *Salmonella*. We report the first case of recurrent NTS in a patient with a history of UC and MS on natalizumab, which was successfully treated with an extended course of rifaximin and temporary cessation of immunosuppressive therapy.

CONFLICT OF INTEREST

Dr. Carl V. Crawford; Speaker's Bureau, Salix Pharmaceuticals

Dr. Ellen Scherl; Research support, Salix Pharmaceuticals, Abbott Laboratories, AstraZeneca, and Janssen Pharmaceuticals; Consultant, Abbott Laboratories, Crohn's and Colitis Foundation of America (CCFA), Janssen Pharmaceuticals, and Salix Pharmaceuticals.

FUNDING

This research was supported by an educational grant from the Louis and Rachel Rudin Foundation.

REFERENCES

1. Haraga A, Ohlson MB, Miller SI. Salmonellae interplay with host cells. Nat Rev Microbiol. 2008; 6: 53-66.
2. Coburn B, Grassl GA, Finlay BB. Salmonella, the host and disease: a brief review. Immunol Cell Biol. 2007; 85: 112-118.
3. Gordon MA. Salmonella infections in immunocompromised adults. J Infect. 2008; 56: 413-422.
4. Dhanoa A, Fatt QK. Non-typhoidal Salmonella bacteraemia: epidemiology,clinical characteristics and its' association with severe immunosuppression. Ann Clin Microbiol Antimicrob. 2009; 8: 15.
5. Soni CR, Kumar G, Bollu PC, Sahota P, Litofsky NS. Salmonella brain abscess in a patient on chronic azathioprine therapy for myasthenia gravis: report of an unusual case and review of literature in the postantibiotic era. J Neurovirol. 2010; 16: 83-92.
6. Giannella RA, Broitman SA, Zamcheck N. Salmonella enteritis. I. Role of reduced gastric secretion in pathogenesis. Am J Dig Dis. 1971; 16: 1000-1006.
7. KUNZ LJ, WADDELL WR. Association of Salmonella enteritis with operations on the stomach. N Engl J Med. 1956; 255: 555-559.
8. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol. 2007; 102: 2047-2056.
9. Delarocque-Astagneau E, Bouillant C, Vaillant V, Bouvet P, Grimont PA, Desenclos JC. Risk factors for the occurrence of sporadic Salmonella enterica serotype typhimurium infections in children in France: a national case-control study. Clin Infect Dis. 2000; 31: 488-492.
10. Mastroeni P, Villarreal-Ramos B, Hormaeche CE. Effect of late administration of anti-TNF alpha antibodies on a Salmonella infection in the mouse model. Microb Pathog. 1993; 14: 473-480.
11. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007; 448: 427-434.

12. García Rodríguez LA, Ruigómez A, Panés J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. Gastroenterology. 2006; 130: 1588-1594.

13. Gradel KO, Nielsen HL, Schønheyder HC, Ejlertsen T, Kristensen B, Nielsen H. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. Gastroenterology. 2009; 137: 495-501.

14. Jess T, Simonsen J, Nielsen NM, Jørgensen KT, Bager P, Ethelberg S, Frisch M. Enteric Salmonella or Campylobacter infections and the risk of inflammatory bowel disease. Gut. 2011; 60: 318-324.

15. Symmons DP, Silman AJ. The world of biologics. Lupus. 2006; 15: 122-126.

16. Sirinavin S, Garner P. Antibiotics for treating salmonella gut infections. Cochrane Database Syst Rev. 2000; : CD001167.

17. Beseghi U, De' Angelis GL. Comparison of two non-absorbable antibiotics for treatment of bacterial enteritis in children. Eur Rev Med Pharmacol Sci. 1998; 2: 131-136.

18. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005; 353: 1912-1925.

19. Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006; 354: 924-933.

20. Ghosh S, Panaccione R. Anti-adhesion molecule therapy for inflammatory bowel disease. Therap Adv Gastroenterol. 2010; 3: 239-258.

21. O'Connor P. Natalizumab and the role of alpha 4-integrin antagonism in the treatment of multiple sclerosis. Expert Opin Biol Ther. 2007; 7: 123-136.

22. Koh A, da Silva AP, Bansal AK, Bansal M, Sun C, Lee H, et al. Role of osteopontin in neutrophil function. Immunology. 2007; 122: 466-475.

Cite this article

Faye A, Metz Y, Hartman B, Crawford CV, Scherl E (2016) Salmonellosis in a Patient on Natalizumab for Ulcerative Colitis and Multiple Sclerosis. JSM Gastroenterol Hepatol 4(1): 1051.