
Caso Clínico / Clinical Case

TYPHOID FEVER – CLINICAL AND ENDOSCOPIC ASPECTS*

A. MURINELLO, A. MORBEY, J. FIGUEIRA COELHO, P. MENDONÇA, A. C. PIRES,
V. MAGALHÃES RAMALHO, N. CARRILHO RIBEIRO, A. LÁZARO, H. PERES, J. NETTA

Resumo

A febre tifóide é uma infecção intestinal causada pela *Salmonella typhi*, manifestada por quadro septicémico, ocorrendo incidência elevada de casos em regiões com deficientes condições sanitárias, através do consumo de água e alimentos contaminados por fezes de indivíduos doentes ou portadores assintomáticos. Em países desenvolvidos os casos verificados são geralmente “importados”. A observação endoscópica das ulcerações da ileocolite tífica tem sido raramente descrita, não havendo referências prévias em Portugal da documentação colonoscópica das ulcerações tíficas. Baseados num caso clínico, os autores fazem uma revisão sobre febre tifóide, no que concerne à patogenia, histopatologia, quadro clínico, aspectos endoscópicos das ulcerações, e terapêutica antibiótica aconselhada nos casos de estirpes de *Salmonella typhi* sensíveis ou resistentes a vários grupos de antibióticos.

Summary

Typhoid fever is an enteric disease due to *Salmonella typhi*, presenting as a septicemic illness, affecting an elevated number of people living in regions with poor sanitary conditions, acquired through the ingestion of water and food contaminated by feces of acutely ill patients or chronic carriers of the microorganism. In developed countries the disease is usually “imported”. Colonoscopic demonstration of ulcerations of typhoid ileocolitis is scarcely referred in medical literature, and there are no previous references to endoscopic aspects of typhoid ileocolitis in Portugal. Based on this, the authors review typhoid fever as far as are pathogeny, pathology, clinical picture and colonoscopic aspects are concerned as well as therapy recommended for susceptible and resistant strains of *Salmonella typhi*.

GE - J Port Gastroenterol 2008; 15: 76-82

INTRODUCTION

Typhoid fever, known previously as “typhus abdominalis” (from the Greek, meaning smoke, fume, stupor) is an enteric fever manifested as a septicemic illness, caused by *Salmonella enterica* serovar *typhi* (*S. typhi*) (Eberth's bacillus), a Gram-negative bacillus able to survive in hostile environments and to proliferate in dairy products, processed meats and shellfish. Worldwide, 15 to 30 million cases of typhoid occur each year, with a half million deaths. High rates of transmission are seen in the Indian subcontinent, Central Asia, Vietnam and Indonesia, sub-Saharan Africa and Latin America, where there are crowding, poor sanitary conditions, deficient areas of sewage disposal and untreated water supplies. In these countries, there are a growing number of resistant strains of *Salmonella typhi* to several antibiotics, complicating the effective treatment of patients⁽¹⁾.

Human beings are the only known reservoir of *Salmonella typhi* and transmission occurs through ingestion of polluted water or food articles contaminated by acutely

ill or chronic carriers of the microorganism⁽²⁾. Raw fruit and vegetables are important vehicles in countries where human feces are used as fertilizer or where contaminated water is used to make fruit look attractive in the market. Shellfish harvested in coastal water polluted by raw sewage may cause outbreaks. Flies carrying bacilli on their feet and proboscises may act as transferring intermediates⁽³⁾.

The pathogenic mechanisms of typhoid fever begin with bacilli ingestion. The infecting dose of *S. typhi* needs to be large to produce illness in healthy individuals, varying between 1000 and 1 million microorganisms⁽³⁾. Microorganisms possessing the Vi antigen have increased infectivity⁽⁴⁾. Gastric hypoacidity favors greater number of microorganisms to enter the small bowel and, recently it was referred the possibility of the association between chronic *Helicobacter pylori* infection and increased risk of typhoid fever due to hypochlorhydria caused by atrophic gastritis⁽⁵⁾. Once in small intestine, the microorganisms multiply in the lumen for a short period and stools can be culture positive during the first four days of the

* Apresentado em forma de Poster no XIII International Congress for Infectious Diseases, Junho 2008 – Kuala Lumpur, Malaysia

incubation period⁽⁶⁾. Then they penetrate rapidly through the intestinal mucosa. The M epithelial cells which overlie the Peyer's patches are the potential sites where *S. typhi* is internalized and transported to the underlying intestinal lymphoid tissue, where, after a brief period of multiplication, the microorganisms enter the blood stream via the thoracic duct (primary bacteraemia), being rapidly filtered out by the reticuloendothelial cells of the liver, spleen and mesenteric lymph nodes⁽⁷⁾. Within the mononuclear phagocytic cells a multiplication of the bacillus occurs followed by invasion (secondary bacteraemia), which initiates clinical illness. During this phase, the microorganisms can invade any organ, mainly the liver, spleen, bone marrow, gallbladder, and Peyer's patches in the terminal ileum. From gallbladder the bacillus follow to the intestine through bile, where they may reinvade the intestinal wall or excreted in the stool. Pre-existing lithiasis of the gallbladder predisposes to chronic biliary infection, leading to chronic fecal carriage⁽⁷⁾.

Invasion of Peyer's patches occurs either during the primary intestinal infection or during the secondary bacteraemia and further seeding occurs through infected bile. Peyer's patches become hyperaemic and hyperplastic, due to infiltration by chronic inflammatory cells and to proliferation of endothelial and reticular cells. Milder cases can revert, but more commonly the process continues, and mucosal necrosis follows, resulting in ulcers of varying extent and depth. The shape of the ulcers is usually ovoid with the longest diameter parallel to the long axis of the gut, so that stricture formation does not occur after healing. The edges are soft, swollen and irregular, but not undermined. The floor is usually smooth and is formed by the muscular coat. Near the ileocecal valve, where perforation occurs more commonly, ulcers become deeper than elsewhere⁽⁸⁾. Large intestine is involved in only a third of the cases, and rarely extensively⁽⁹⁾. The lesions tend to decrease in severity distally to the ileocecal valve. When an ulcer erodes into a blood vessel, severe hemorrhage results^(10,11) and transmural perforation leads to peritonitis⁽¹²⁾.

The authors report for the first time in Portugal the colonoscopic aspect of typhoid ulcers in a case of typhoid ileocolitis on a white woman who acquired typhoid fever after a sojourn in India.

CASE REPORT

A 36-year-old unmarried white woman was admitted to our Unit in 2007 JUNE 04, after a sojourn in South of India (state of Kerala) from 2007 APRIL 23 to 2007 MAY 24, in a monastery, where she did several domestic activities and was in contact with a great number of people

living in a community of around 3.000 residents. Among them there were some people with tuberculosis. She was vegetarian and ingested occasionally raw vegetables, and a great amount of rice. Water was filtered, but sometimes she brushed her teeth with non-drinking water. She also consumed potentially unpasteurized milk and yogurt drinks. On the area there were many flies. She referred to have been bitten several times by mosquitoes. It was fairly common to see rats in the area. She denied to have done malaria prophylaxis and she had no vaccination before this sojourn. Five days after arriving in Portugal, the patient began to feel unwell, tired and slightly febrile in the afternoon (37.7° C at MAY 31). She came for the first time to the Emergency Room of our Hospital on JUNE 01, with fever (38° C). Physical examination was otherwise normal. LAB tests showed no anemia and no leucopenia or thrombocytopenia. *Plasmodium* was not detected; biochemistry was normal. She was discharged. On the afternoon of JUNE 03 her axillary temperature was 39° C, she was feeling more tired and anorectic, but denied any other symptoms, including constipation and diarrhea. At admission, on the morning of JUNE 04 (5th day of disease), axillary temperature was 38° C, she was slightly dehydrated, with low blood pressure and increased heart rate. There were no other abnormal signs on physical examination, except a slightly painful palpation of right iliac fossa, without peritoneal irritation. Blood tests revealed ESR 46 mm; PCR 6.80 mg/dL (N < 1); AST 56 U/L (17-59); ALT 45 U/L (21-72); LDH 1164 U/L (313-618). Several blood serologic tests were negative (*Entamoeba histolytica*, *Schistosoma*, *Brucella*, *Lep-tospira*, VDRL, Widal, HAV, HBV, HCV, HIV). Urine and stool cultures were negative, as well as parasitological stool examination. Chest x-ray was normal. Meanwhile, the clinical picture evolved with sustained fever (38.5-39.6° C) and complaints of defective memory and confusion. Abdominal US revealed several slightly enlarged lymphatic nodes in the ileocecal region (Figure 1a). Abdominal CT scan showed discrete but diffuse thickening of the wall of the right colon, exuberant parietal right colon vascularization, besides multiple small lymphadenopathies at the ileocecal region (Figures 1b and 1c), along the root of the mesentery (12 mm) and proximal aortocava area (12 mm). Slight hepatomegaly and a small volume of ascitic fluid in the pelvis were noted. These aspects were in favor of an exuberant acute colitis with loco-regional component of lymphatic gland hypertrophy. Colonoscopic examination was performed in order to exclude other entities like Crohn's disease, tuberculosis ileocolitis, and lymphoma. Multiple ulcers were seen on the proximal third of the descending colon, transverse colon, ascending colon and caecum, some of them with furry aspects, parallel to the long axis of the intestine,



Figura 1a - Abdominal US: multiple lymphadenopathy in the ileocecal region.

Figura 1b - Abdominal CT scan: multiple lymphadenopathy in the ileocecal region.

Figura 1c - Abdominal CT scan: hypervascularization and inflammatory thickening of the wall of the caecum.

with hyperemia of the underlying mucosa. Some of the ulcers showed a punched-out aspect (Figures 2a, 2b, 2c, 2d and 2e). The terminal ileum also had several similar

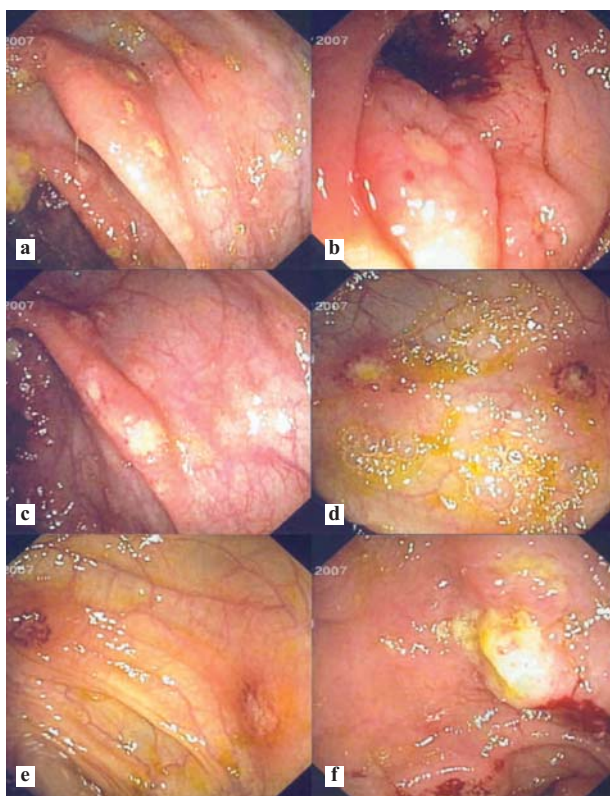


Figura 2a - Colonoscopy: multiple ulcers in the proximal third of the ascending colon.

Figura 2b - Colonoscopy: "punched-out" ulcers with furry aspect in the same area.

Figura 2c - Colonoscopy: several ulcers in the transverse colon, running parallel to the long axis of the colon.

Figura 2d and 2e - Colonoscopy: two ulcers surrounded by hemorrhagic mucosa located to the splenic angle of the colon and in the descendant colon.

Figura 2f - Colonoscopy: giant ulcer of the mucosa of the terminal ileum with furry aspect, and with intense hyperemia and edema of the adjacent mucosa.

ulcers (Figure 2f). Biopsies of ileal and colonic ulcers revealed aspects of necrotizing ulcers with fibrin and heavy mixed inflammatory infiltrate. Besides that, on the ileon there was *villi* atrophy (Figure 3a) and on the colon crypt atrophy and active areas of cryptitis and crypt abscesses. (Figures 3b and 3c). Treatment for presumed typhoid fever was given (1 g of e.v. ceftriaxone two times daily) immediately after colonoscopy, on the afternoon of JUNE 08. The diagnosis was confirmed by positive blood culture for *Salmonella typhi* on JUNE 09. After 6 doses of ceftriaxone, fever began to decrease slowly and the patient started to feel better. At that time patient asked to be discharged from the hospital, and therapy was changed to oral ciprofloxacin. Temperature continued to decrease gradually, and she became afebrile 15 days after the initiation of therapy. Stool cultures were negative 45 days after the end of therapy. Already in Portugal and after knowing the diagnosis, she realized that several people with whom she traveled to the north of the state of Kerala, also had typhoid fever.

DISCUSSION

Endoscopic demonstration of colonic and terminal ileum lesions of typhoid by colonoscopy is scarcely reported in medical literature, as these examinations are only advised when the etiological diagnosis is not yet established. Ulcerations generally occur in the terminal ileum, cecum and ascending colon, and rarely in the left side of the colon⁽⁹⁾. Ulcer margins are edematous and raised, so that the ulcers are elevated above the normal-appearing surrounding mucosa, presenting as umbilicated, ulcerated mounds, the so-called "punched-out" ulcers⁽¹³⁾. Some of the ulcers are discrete, white, with furry appearance. Several oedematous hyperaemic mucosal patches with haemorrhagic spots or shallow erosions can be seen⁽¹⁴⁾. The typical ulcers are round or oval, oriented along the long axis of the bowel^(15,16). Some ulcers are arranged in an ir-

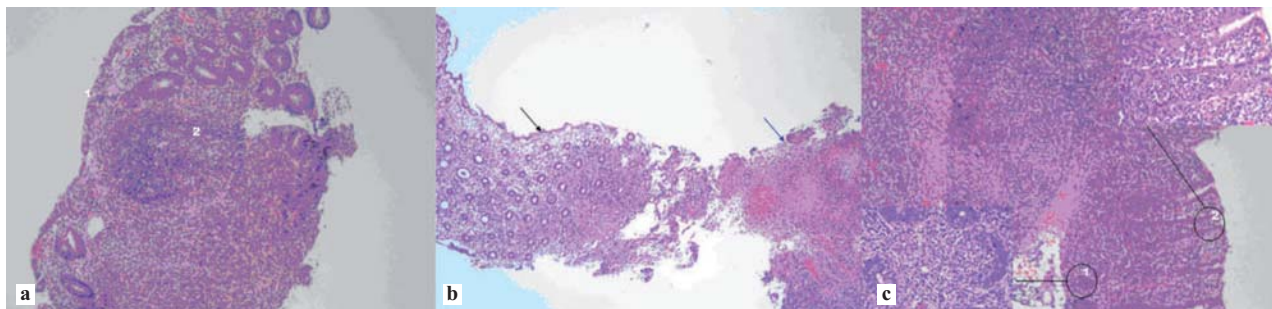


Figura 3a - Histopathology (HE - 100x): Mucosal fragment of terminal ileum, with atrophy of villi (1), a voluminous lymphoid follicle (2), and dense infiltration of mixed inflammatory cells in lamina propria.

Figura 3b - Histopathology (HE - 50x): Mucosal fragment of distal intestine, with crypt atrophy (black arrow), an ulceration area (blue arrow), and a dense infiltration of mixed inflammatory cells in lamina propria.

Figura 3c - Histopathology - (HE 100x): Intense inflammatory reaction, with abscess of the mucosal crypts (inserts 1- HE 400x; 2-HE 400x).

regular fashion⁽¹⁷⁾. The ulcers are not undermined as the ulcers of amoebiasis, nor linear in shape, which is typically observed in Crohn's disease. In tuberculosis ileocolitis transverse and linear ulcers can present along with nodules, strictures and polypoid lesions.

The distribution of ulcers corresponds to the presence of lymphoid aggregates in the intestine, therefore most cases of hemorrhage and perforation occur in the vicinity of the terminal ileum^(18,19). These colonoscopy findings can be explained on the basis of the route of infection and the structure of the lymphatic ducts in the ileocecal region, since lymphatic ducts are associated with either the main or the marginal arteries^(8,13). Due to its abundant lymphatic tissue, *Salmonella typhi* in the ileocecal region spread proximally and ran along the marginal arteries, which explain its distribution in other segments of the colon.

Differential etiological diagnosis of ulcers with a discrete or punched out appearance include ulcers due to *Yersinia enterocolitis*, *Mycobacteria tuberculosis*, *Entamoeba histolytica*, *Campylobacter*, other *Salmonella*, *Aeromonas hydrophilia*, *Histoplasma capsulatum*, *Cytomegalovirus* in AIDS patients, and also Behcet's disease, vasculitis, Crohn's disease, and NSAIDs use^(9,20,21).

Microscopic examination of biopsies of these ulcers reveals acute colitis with ulceration, a polymorphic inflammatory infiltrate with predominance of swollen histiocytes and polymorphonuclear leukocytes. Plasma cells and eosinophilia can also be seen. Sometimes Gram stain reveals the presence of typical Gram-negative bacillus⁽⁷⁾. Ulcer bleeding can be either severe or slow oozing. The incidence of hemorrhage was about 20% before the introduction of the antibiotics, but it has declined since then. However in a few symptomatic cases it may be the initial manifestation^(13,14). The more frequent localization of bowel perforation is on the anti-mesenteric side of the intestine at approximately 80 cm from the ileocecal valve⁽²²⁾. It is disturbing that several authors are seeing now more

perforations per patient, and more involvement of the colon^(11,23).

The proposed pathogenesis is the unique relationship between *S. typhi* and macrophages in the liver, spleen, intestinal lymphoid follicles, and mesenteric lymph nodes. Macrophages cells synthesize functionally active cytokines (TNF- α , IL-1, interferon- α and β), and are an important source of arachidonate metabolites and reactive oxygen intermediates. These products can lead to cellular necrosis, recruitment of other inflammatory cells, stimulation of the immune system, vascular instability, to initiation of the clotting mechanism, bone marrow depression, fever and other abnormalities associated with typhoid fever⁽²⁴⁾.

After an incubation period of generally 10 to 12 days, with variations from 5 to 25 days, clinical illness begins usually insidiously. Clinical manifestations of infection in travelers to endemic areas of typhoid are usually different from local resident cases. Despite unvaccinated travelers have no pre-existing immunity, usually their clinical manifestations are not as serious as in patients of endemic areas, probably because they have in general more rapid and readily available access to medical care, and they might consume smaller amount of contaminated food due to hygienic precautions⁽²⁵⁾.

The clinical presentation of typhoid fever is variable and is determined by the strain of *Salmonella typhi*, the number of ingested microorganisms, general and nutritional condition and immunologic status of the patient, and, possibly, the genetic makeup of the host⁽⁶⁾. Hospital-based physicians will see typhoid patients who are much sicker, have a greater range of symptoms, signs, and complications, with a case fatality rate from 1% to 30%⁽⁷⁾. However, many outpatients in clinics in endemic areas of developing world are only moderately ill, with fewer than 10% requiring hospitalization and a case-fatality rate of less than 1%⁽⁷⁾.

Most descriptions on text books are related to serious disease in endemic countries, and manifestations are divided in four periods, each of approximately one week's duration^(1-3,7,26,27). The disease begins insidiously, with malaise, chills, weakness, anorexia, headache, epistaxis, non-productive cough, and abdominal pain. Constipation is more common than diarrhea. Temperature rises steadily reaching 40° C around the 4th or 5th day. Pulse may be dicrotic in some patients or slow, related to body temperature. During the first week blood cultures are normally positive. At the end of the first week, hepatomegaly, splenomegaly and roseola typhica may appear. With increasing severity of symptoms and signs by the second week, "pea soup" stool diarrhea can occur, and the abdomen is distended and very tender; mental state deteriorates progressively from a period of defective memory to complete confusion, torpor and stupor. The patient's face is pale but with a malar "flush", expression is dull, pupils are dilated, lips are dry and the tongue is furred. Temperature reaches its maximum, remaining at a plateau. Serious complications, hemorrhages and perforations of the ulcers can occur at the end of the second week and during the third, after which, improvement begins at the end of the third week or at the fourth week of the disease course⁽⁸⁾. Rare complications can occur such as lung abscesses, thrombosis (femoral), cholecystitis, bone lesions (abscesses, periostitis), myositis, vulvitis, orchitis, mastitis, meningitis, peripheral neuritis, eyelid and orbital abscesses, orbital thrombosis, etc⁽⁸⁾.

According to several series in endemic areas of developing world, patients admitted to hospital usually present with: fever and weakness 99%, anorexia and headache 85%, dizziness 80%, abdominal pain 50%, nausea 50%, chills 50%, diarrhea 45%, constipation 40%, cough or chest discomfort and vomiting 35%, and myalgia/arthralgia in 35%, confusion 25%, sore throat 20%, hearing loss 15%, blood in stool or melena 12%, epistaxis 10%, dysuria 2%, and seizures 2%. Physical signs frequency: fever 98%, coated tongue 95%, apathy 70%, hepatomegaly 50%, abdominal pain 45%, rose spots 0-50%, toxicity 45% (severe 10%), splenomegaly 35-50%, disorientation 25%, relative bradycardia 15%, rales or ronchi 15%, delirium 15%, decreased hearing 10%, stiff neck 10%, stupor 2%, focal neurological findings 1%⁽⁷⁾.

Extreme weakness, heart failure due to myocarditis, pneumonia, and intestinal hemorrhage and perforation are usually causes of death⁽⁸⁾. The average case fatality rate is less than 1 per cent, but the rate varies considerably among different regions of the world. Mortality is much more frequent in children under one year of age and among elderly people. However the most important cause of poor outcome is a delay in instituting effective antibiotic treatment. Relapses can occur after a week or two

of apyrexia, and may supervene even in patients in whom correct antibiotic treatment was performed. Chronic carrier states occur mostly in patients with previous gallstones (2-5% of cases), even after correct treatment^(7,8). Biliary carriage is defined as a continuous shedding of the microorganism for more than a year⁽²⁵⁾.

Diagnosis depends on the demonstration of positive cultures of *Salmonella typhi* in blood, and in the urine or stools. When patients have already initiated antibiotics, bone marrow cultures provide a better chance of recovery the microorganism, with a success rate of up to 80% (10 bacteria/ml bone marrow versus 1/ml peripheral blood)⁽²⁵⁾.

High agglutinin titers in the Widal test of the order of 1:320 during the second week of the disease, in an adequate epidemiologic context of probable typhoid infection, favor the diagnosis of typhoid fever⁽²⁵⁾. Meanwhile in regions with limited resources, rapid and simple tests to detect anti-*Salmonella typhi* antibody against lipopolysaccharide or outer membrane protein may replace the less accurate Widal test⁽²⁸⁾. DNA probes and PCR for detection of *Salmonella typhi* in blood appear to be more rapid and sensitive than standard culture, but are not yet commercially available and have a prohibitive cost in many areas where typhoid is endemic⁽²⁹⁾.

Leucopenia and thrombocytopenia are common and liver enzymes can be moderately elevated. Barium meal and enema are not usually done for the diagnosis of typhoid ileocolitis, but they can show the typical typhoid ulcerations. CT scan can reveal inflammatory thickening of the wall and ulcerations of the intestine, together with adenitis of the mesenteric root.

Referring to different and more serious manifestations in typhoid ileocolitis in cases occurring in a particular area, Adeniran⁽²³⁾ in Nigeria raised several questions: is the pathology of typhoid changing due to different pathogenic *Salmonella typhi*? Are the patients getting less immune? Is the environment changing? Is malnutrition or HIV complicating the problems? Are there inappropriate use of antibiotics and undue delays from the referring hospitals? Is the resistance to antibiotics requiring new drugs? Are there some yet unidentified associated microorganisms causing the colonic perforations? Is it man or the microorganisms or the environment changing the goal posts?

It is worth to mention that sometimes an uncommon form of evolution can occur, the so-called prolonged salmonellosis, because of previous hepatosplenic or hepatointestinal forms of schistosomiasis. In these patients, *Salmonella typhi* multiplies inside the *Schistosoma* and possibly on the reticuloendothelial system, causing frequent bacteraemias, perpetuating the disease with a possible evolution of several months to one or two years duration⁽²⁶⁾.

Therapy of typhoid fever is becoming more difficult today, because of the increasing number of areas with occurrence of cases of multi-drug resistant strains to several antibiotics previously utilized in typhoid fever – chloramphenicol, ampicillin or co-trimoxazole^(30,31). Multi-drug-resistant strains require extensive therapies that are less effective and result in higher stool carriage rates with a greater transmission potential⁽²⁵⁾. The complete genome sequence was already determined for a multi-drug resistant strain of *Salmonella enterica* serotype *typhi* (CT18)⁽³²⁾. These microorganisms have several large insertions in its genome, termed *Salmonella* pathogenicity islands, which encode genes important for survival in the host, with importance to its pathogenicity⁽³²⁾.

The introduction of fluoroquinolones was a major advance, but unfortunately there is an increasing number of fluoroquinolone-resistant strains⁽³³⁻³⁵⁾. Although many laboratories use disk diffusion for sensitivity evaluation, this test does not reflect true quinolone sensitivity by itself; only nalidix acid sensitivity confirms true quinolone sensitivity. Determining minimum inhibitory concentrations gives a more predictable measure of antibiotic resistance⁽²⁵⁾. These quinolone-resistant strains were noted to be sensitive to ceftriaxone, cefixime, and azithromycin but the clinical response is slower, with fever clearance taking 7 days or more and failure rates of greater than 20%⁽³³⁾. Currently, the recommendation for first-line therapy is ceftriaxone 2 g daily for 10 days⁽³⁶⁾. Meanwhile if the isolates have been found to be fluoroquinolone sensitive, standard doses of fluoroquinolones may be used for 10 to 14 days, some authors presenting good results with a course of only 5 days' duration⁽³⁷⁾.

The use of glucocorticosteroids has been advocated in the treatment of severe typhoid fever based upon a study in Jakarta that showed a significant reduction in mortality among patients with severe typhoid fever (i.e. associate delirium, obtundation, stupor, coma, or shock) treated with chloramphenicol and dexamethasone compared with chloramphenicol-treated control patients (case fatality rate: 10% vs. 56%)⁽³⁸⁾. This indication was recently corroborated by the "Antimicrobial Agents Committee of The Infectious Diseases Society of North America"⁽³⁹⁾.

Management of gastrointestinal bleeding complicating typhoid fever is usually conservative, although massive bleeding may, at times, require surgery. Severe intestinal hemorrhage occurred in 3% to 27% of patients with enteric fever in a series from Tokyo⁽⁴⁰⁾. In most reports, surgical resection was an effective treatment in cases of severe bleeding⁽³⁹⁾. Some authors refer to the possibility of obtaining good results with endoscopic haemostatic therapy in cases of moderate ileal and colonic hemorrhage from typhoid ulcers^(14,21).

When intestinal perforation occurs surgery is indicated. Double-layer closure, ileal resection, right hemicolectomy, and temporary ileostomy and colostomy, are surgical methods with specific indications, depending on the severity of perforations. It is good practice to associate antibiotics for gram-negative and anaerobic microorganisms together with peritoneal lavage^(11,23).

To our knowledge the case of our patient is the first to be reported in Portugal, with demonstration of the typical endoscopic aspects of the ileal and colonic ulcers of typhoid ileocolitis, together with imagiologic views revealing aspects compatible with acute inflammatory colitis and mesenteric adenitis.

BIBLIOGRAPHY

1. Richens J, Parry C. Typhoid and paratyphoid fever. In: Warrel DA, Cox TM, Firth JD, Benz Z, Jr EJ, eds. Oxford Textbook of Medicine. 4th ed. Oxford: Oxford University Press; 2003. p. 503-507.
2. Christie AB. Typhoid and paratyphoid fevers. In: Christie AB, ed. Infectious Diseases: Epidemiology and Clinical Practice. 3rd ed. Edinburgh: Churchill Livingstone; 1980. p. 47-102.
3. Gillespie SH. Salmonella infections. In: Cook GC, Zumla A, eds. Manson's Tropical Diseases. 21st ed. London: WB Saunders/Elsevier; 2003. p. 937-949.
4. Hornick RB, Greiseman SE, Woodward TE, et al. Typhoid fever: pathogenesis and immunological control. *New Engl J Med* 1970; 283: 686-91.
5. Bhan MK, Bahl R, Sazawal S, Sinha A, Kumar R, Mahalanabis D, et al. Association between *Helicobacter pylori* infection and increased risk of typhoid fever. *J Infect Dis* 2002; 186: 1857-60.
6. Gillespie SH. Salmonella. In: Emerson AM, Hawkey PM, Gillespie SH, eds. Principles and Practice of Clinical Bacteriology. 1st ed. Chichester: Wiley; 1997. p. 399-412.
7. Epstein JE, Hoffman SL. Typhoid fever. In: Guerrant RL, Walker DH, Weller PF, eds. Tropical Infectious Diseases: Principles, Pathogens and Practice. 2nd ed. Philadelphia: Churchill Livingstone/Elsevier; 2006. p. 220-240.
8. Netter FH. Typhoid fever. In: Oppenheimer E, ed. The Ciba Collection of Medical Illustrations – Part II, vol 3 – Digestive System. New York: Ciba Pharmaceutical Co.; 1962. p. 149-151.
9. Hepps K, Sutton FM, Goodcane RW. Multiple left-sided colon ulcers due to typhoid fever. *Gastrointestinal Endoscopy* 1991; 37: 479-80.
10. Sood A, Midha V, Sood N. Massive hemorrhage from colonic ulcers in typhoid fever. *Indian J Gastroenterol* 2001; 20:80.
11. Herrán L, Flores A, De Benedetti ME, de los Ríos R, Gotuzzo E. Reaparición de formas graves de tifoide: a propósito de un caso de sangrado masivo gastrointestinal. *Rev Gastroenterol Peru* 2007; 27: 62-67 (spanish).
12. Uddin N, Vihan MA, Tasneem Z. Colonic perforations in enteric fever. *J Coll Physicians Surg Pak* 2004; 14: 634-5.
13. Kasamaki S, Sato T, Ochiari T, Shijo H, Kudo K, Suda S. A case of typhoid ulcers followed up with colonoscopy. *Digestive Endoscopy* 2000; 12: 196-8.
14. Lee JH, Kim JJ, Jung JH, Lee S-Y, Bae MH, Kim Y-H, et al. Colonoscopic manifestations of typhoid fever with lower gastrointestinal bleeding. *Dig Liv Dis* 2004; 36: 141-6.
15. Smith JH. Typhoid fever. In: Binford CH, Connor DH, eds. Pathology of Tropical and Extraordinary Diseases. Vol 1. 1st ed. Washington: Armed Forces Institute of Pathology; 1976. p. 123-129.

16. Reyes E, Hernandez J, Gonzalez A. Typhoid colitis with massive lower gastrointestinal bleeding. *Dis Colon Rectum* 1986; 29: 511-4.
17. Kume K, Kubo K, Murata I, Yoshikawa I, Nakamura H, Hata H, et al. Endoscopic diagnosis in typhoid fever. *Endoscopy* 2000; 32: S31.
18. Kang JY. Endoscopic diagnosis of ileal ulceration in typhoid fever. *Gastrointestinal Endoscopy* 1988; 34: 442-3.
19. Wong S-Y, Fook-Hong Ng, Know K-H, Chow K-C. Skip colonic ulceration in typhoid ileocolitis. *J Gastroenterol* 1999; 34: 700-01.
20. Zuckerman M, Meza AD, Ho H, Menzies IS, Dudrey EF. Lower gastrointestinal bleed in a patient with typhoid fever. *Am J Gastroenterol* 2000; 95: 843-5.
21. Garg PK, Bathia V, Tandon RK. Endoscopic therapy is effective for bleeding ileal ulcer. *Gastrointestinal Endoscopy* 2003; 57: 797-9.
22. Mock CN, Amatrul J, Kissler LE. Improvement in survival from typhoid ileal perforation. Results of 221 operative cases. *Ann Surg* 1992; 215: 244-9.
23. Adeniran JO, Taiwo JO, Abdur-Rahman LO. Salmonella intestinal perforation: (27 perforations in one patient, 14 perforations in another). Are the goal posts changing? *J Indian Assoc Pediatr Surg* 2005; 10: 248-51.
24. Hornick RB, Greisman S. On the pathogenesis of typhoid fever. *Arch Int Med* 1978; 138: 357-9.
25. Connor BA, Schwartz E. Typhoid and paratyphoid fever in travelers. *The Lancet Infectious Diseases* 2005; 5: 623-8.
26. Bastos CO. Febre Tifóide. In: Veronesi R, ed. *Doenças Infecciosas e Parasitárias*. 6ª ed. Rio de Janeiro: Guanabara Koogan; 1976. p. 406-417 (portuguese).
27. Pegues DA, Ohl ME, Miller SI. Salmonella species, including Salmonella typhi. In: Mandell GL, Bennet JE, Dolin R, eds. *Mandell, Douglas, Bennet's Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia: Elsevier/Churchill Livingstone; 2000. p. 2636-2650.
28. Bhutta ZA, Mansurali N. Rapid serologic diagnosis of pediatric typhoid fever in an endemic area: a prospective comparative evaluation of two dot-enzyme immunoassays and the Widal test. *Am J Trop Med Hyg* 1999; 61: 654-7.
29. Chandhary R, Laxmi BV, Nisar N, et al. Standardisation of polymerase chain reaction for the detection of Salmonella typhi in typhoid fever. *J Clin Pathol* 1997; 50: 437-9.
30. Mirza SH, Beeching NJ, Hart CA. Multi-drug resistant typhoid: a global problem. *J Med Microbiol* 1996; 44: 317-9.
31. Gupta A. Multi-drug-resistant typhoid fever in children: epidemiology and therapeutic approach. *Pediatr Infect Dis J* 1994; 13: 134-40.
32. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *New Engl J Med*. 2002; 347: 1770-82.
33. Parry CM, Wain J, Chin NT, et al. Quinolone-resistant Salmonella typhi in Vietnam. *Lancet* 1998; 351: 3.
34. Mermin JH, Villar R, Carpenter J, et al. A massive epidemic of multi-drug resistant typhoid fever in Tajikistan associated with consumption of municipal water. *J Infect Dis* 1999; 17: 1416-22.
35. Murdoch DA, Banatvala NA, Bone A, et al. Epidemic ciprofloxacin resistant Salmonella typhi in Tajikistan. *Lancet* 1998; 351: 339.
36. French RW, Nakhla I, Sultan Y, et al. Azythromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clin Infect Dis* 2000; 31: 1134-8.
37. Alam MN, Hag SA, Das KK, et al. Efficacy of ciprofloxacin in enteric fever: comparison of treatment duration in sensitive and multi-drug resistant Salmonella. *Am J Trop Med Hyg* 1995; 53: 306-11.
38. Butler T, Islam A, Kabir I, Jones PK. Patterns of morbidity and mortality in typhoid fever dependent on age and gender: review of 552 hospitalized patients with diarrhea. *Rev Infect Dis* 1991; 13: 85-90.
39. McGowan JE, Chesney PJ, Crossley KB, et al. Guidelines for the use of glucocorticosteroids in the management of selected infections. *J Infect Dis* 1992; 165: 1-13.
40. Hoshimo Y, Masuda G, Negfishi M, Ajisana A, Imamura A, Hachimori K, et al. Clinical and bacteriological profiles of patients with typhoid fever treated during 1975-1998 in the Tokyo Metropolitan Komagome Hospital. *Microbiol Immunol* 2000; 44: 577-83.