Clinicopathological study of Ileal perforation: study in tertiary center

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ABSTRACT

Background: The objective of this study was to evaluate the clinicopathological characteristics in ileal perforations because of confusion and controversy over the diagnosis and optimal surgical treatment of terminal ileal perforation - a cause of obscure peritonitis. Perforation of terminal ileum is a cause for obscure peritonitis with severe toxic state, there may be obscured clinical features with resultant delays in diagnosis and adequate surgical intervention.

Methods: A prospective study was conducted in Victoria Hospital and Bowring and Lady Curzon Hospital attached to Bangalore Medical College and Research Institute over a period of 5 years from June 2011 to May 2015. A total of 136 patients presented in this period with hollow viscus perforation and out of these 64 patients had ileal perforation alone on exploratory laparotomy. Ileal perforations account for about 20 percent of all cases of hollow viscus perforation. Emergency exploratory laparotomy was done and perforation was identified, edge biopsy was taken in all cases and the perforation was closed in two layers and resection anastomosis was done in stricture with perforation. Histopathological report was reviewed following surgery.

Results: A total of 64 patients with ileal perforation were included in the study of which 52 were males and 12 were females accounting for 81.25 percent and 18.75 percent respectively. The causes for perforation were enteric fever (82.81%), nonspecific inflammation (9.38%), and tuberculosis (7.81%). Simple closure of the perforation (74.58%) and the remaining primary resection and anastomosis were the mainstay of the surgical management.

Conclusions: The common pathology of ileal perforation is Typhoid or Enteric fever, Non-specific ulcer, Tuberculosis and others. Intestinal complication of typhoid fever are quite common in developing countries. Nonspecific inflammation of the terminal ileum was other predominant cause operative findings were similar to that of typhoid fever but no laboratory evidence of the disease was found. Intestinal tuberculosis can mimic many conditions.

Keywords: Ileal perforations, Typhoid ulcers, Tuberculosis

INTRODUCTION

Hollow viscus perforation leading to peritonitis is one of the commonest emergency surgeries conducted in a surgical practice for a case of acute abdomen.¹ It is the second most common cause for acute abdomen following appendicitis. Perforation as a cause of acute abdomen accounts for 30-40% of the total cases of acute abdomen presenting to a surgical emergency.² Among the cases of hollow viscus perforation duodenal and gastric perforations are the commonest accounting to almost 60-80% in some series, followed by ileal, appendicular and large bowel.
The incidence of perforation is on the rise due to the increased prevalence of gastritis in the population and also due to the increased use of over the counter NSAIDs which abolish the gastro-protective effects of prostaglandins. The incidence of Ileal perforation is also increasing mainly due to increased number of people presenting to the emergency department and also due to better diagnosis and improved reporting of cases. Ileal perforations account for about 20% of all cases of hollow viscus perforation. Among the causes for Ileal perforations, typhoid Ileal perforations are the commonest followed by tubercular and other etiologies.

Emergency exploratory laparotomy and perforation closure is the mainstay of treatment when a hollow viscus perforation is diagnosed on an erect X-ray abdomen. Although the mortality rates due to perforation has largely come down owing to an early diagnosis and treatment, the morbidity resulting from the condition and concomitant surgery still remains high. We try to study the clinicopathological factors in Ileal perforations.

METHODS

A prospective study was conducted in Victoria Hospital and Bowring and Lady Curzon Hospital attached to Bangalore Medical College and Research Institute over a period of 5 years from June 2011 to May 2015. A total of 136 patients presented in this period with hollow viscus perforation and out of these 64 patients had Ileal perforation alone on exploratory laparotomy and were included in the study.

Inclusion criteria

- Patients presenting to our hospital with signs of hollow viscus perforation
- Patients with an intra-operative finding of Ileal perforation
- Patients who consented for emergency exploratory laparotomy.

Exclusion criteria

- 1 Patients with hollow viscus perforation other than Ileal perforation
- 2 Patients who refused to undergo exploratory laparotomy.

All patients underwent an emergency exploratory laparotomy via a midline incision under general anaesthesia or epidural analgesia. The perforation was identified, edge biopsy was taken in all cases and the perforation was closed in two layers. The first layer of full thickness interrupted sutures of polyglactin or polydioxanone 3-0 and a second layer of interrupted seromuscular silk 3-0. A thorough peritoneal lavage was given. In case there was a perforation associated with a stricture, either a strictureplasty or a primary resection and anastomosis was done. Wound was then closed in layers. The edge biopsy specimen was sent for histopathological examination. The post-operative complications such as wound infection, fever, anastomotic leak, entero-cutaneous fistula, wound dehiscence were noted. All patients were tested for Widal positivity and were started on anti-Salmonella treatment if it was positive or if there was a strong suspicion based on intra-operative or histo-pathological findings. Patients were discharged after 5 days if the post-operative was uneventful. All patients were followed up for a period of 6 months.

RESULTS

A total of 64 patients with Ileal perforation were included in the study of which 32 were males and 12 were females accounting for 81.25% and 18.75% respectively. The most common age group in our study was 40-50 years with 24 patients belonging to this age group, followed by 30-40 years. The age range was 21-67 years and the median age was 43 years. The most common symptom was pain abdomen which was present in all the patients (100%). The next common symptom was vomiting seen in 44 out of 64 patients (68.75%) followed by fever seen in 38 out of 64 patients (59.38%).

![Figure 1: Demography; age/sex-bar diagram.](image)

![Figure 2: Bar diagram showing different type of perforations.](image)

35 patients presented within the first 2 days of onset of symptoms (54.69%), 25 (39.06%) presented on 3rd to 7th day, while 4 patients presented after a week of onset of symptoms (6.25%). On examination, localized or generalized tenderness was present in 62 patients (96.86%). Guarding and rigidity was found in 50 out of 64
patients (78.13%). Absent bowel sounds was found in 36 out of 64 patients (56.25%). Air under diaphragm on erect X-ray abdomen was found in 56 patients (87.5%).

On laparotomy, ileal perforation alone was found in 59 patients (92.19%). Two patients had a stricture just distal to their perforation (3.125%), two had tubercles studded on the mesentery and the surface of the bowel (3.125%) and one had extensive adhesions between the bowel loops (1.56%) along with the perforation.

Among the 59 cases with ileal perforation alone, a solitary perforation was found in 44 patients (74.58%), 2 perforations in 10 patients (16.95%) and 3 or more perforations in 5 patients (8.47%). In cases with 2 or fewer perforations, a primary closure was done and in the rest a primary resection and anastomosis was done. Among the 59 cases, 53 (82.81%) were found to be secondary to typhoid fever based on antigen detection or histopathological findings and the other 6 (9.38 %) were diagnosed to be non-specific. The other 5 cases (7.81%) were found to be secondary to granulomatous disease most likely to be abdominal tuberculosis.

All patients were given antibiotics post operatively specific to their condition or based on culture and sensitivity report of the peritoneal fluid in non-specific cases. Patients were followed up in the post-operative period for the development of complications. 12 out of 64 patients had a wound infection (18.75%), 5 had an anastomotic leak or an entero-cutaneous fistula secondary to re-perforation or leak from the old perforation site (7.81%) of which 2 required re-laparotomy. 10 patients had sepsis continuing post operatively as manifested by fever and increased leucocyte count. Lower respiratory infection was seen in 16 patients (25%) manifested by cough and crepitations. Wound dehiscence was seen in 1 patient (1.56 %). 2 patients (3.13 %) developed signs of sepsis and MODS post operatively and could not be revived, one of whom expired on the first post-operative day and the other on day 3.

All patients were discharged after 5 days in case of uneventful post-operative period and then followed up for a total duration of 6 months. Histopathological report was reviewed following surgery.53 cases were diagnosted to be widal positive these cases on histopathological examination showed areas of necrosis with deeper tissue showing hyperplasia of lymphoid tissue. Few cases showed macrophages containing engulfed nuclear debris and features maybe consistant with typhoid ulcer was suggested. 6 cases were diagnosted as Non-specific ulcer on histopathological examination. These cases on microscopy showed the ulcer covered by necrotic purulent exudate with underlying granulation tissue and acute inflammation cell infiltration. 5 cases were diagnosed as granulomatous inflammation. Biopsy showed ulceration of mucosa ulceration of mucosa and sub-mucosa with trans-mural chronic inflammatory cell infiltration composed of lymphoid cells, multiple caseating and non-caseating granulomas. The granulomas were composed of epithelioid cells and langhans type of giant cells.

**Figure 3: Non-specific ulcer.**

Thin layer of necrotic fibrinous purulent exudate covers the ulcer base. Beneath this is a zone of infiltrate consisting chiefly of neutrophils, below this is a zone of granulation tissue formation which is infiltrated by lymphocyte histiocytes. Fibrocollagenous scar is seen deeper to the granulation tissue. The blood vessels in the scar are thick allied and often thrombosis.

**Figure 4: Non-caseating granulomas.**

Histologically there is ulceration of mucosa and submucosa. Transmutably seen are a large number of caseating and non-caseating, often confluent granulomas of variable size. The granulomas are composed of epithelioid cells with a peripheral zone of lymphocytes and langhan's giant cells, and surrounding fibrosis.

**Figure 5: Hypertrophied payer’s patch in the ileum with ulceration of mucosa.**
DISCUSSION

The terminal ileal perforation presents a diagnostic dilemma to the surgeon. Non-traumatic terminal ileal perforation is still common as a cause for obscure peritonitis in developing and underdeveloped world.\textsuperscript{1} In developed countries, spontaneous Ileal perforations are reported to be mostly because of foreign bodies, radiotherapy, drugs, Cohn’s disease and malignancies.\textsuperscript{2} The common pathology of Ileal perforation are typhoid, nonspecific ulcer, obstruction, tuberculosis, radiation enteritis.\textsuperscript{1} In this study among the 59 cases, 53 (82.81 %) were found to be secondary to typhoid fever based on antigen detection or histo-pathological findings and the other 6 (9.38%) were diagnosed to be non-specific

Typhoid fever also known as enteric fever, a severe febrile infectious disease caused by Salmonella typhi and salmonella para typhi occurs in areas where poor socioeconomic levels and unsanitary environment. The majority of cases in endemic countries are due to S. typhi, while infection by S. paratyphi is more common among travellers.

After ingesting contaminated food or water, during the first week of infection multiplication of bacteria occurs in the reticuloendothelial system during an incubation period of 1-14 days. During the enteric phase of typhoid fever, distinctive lesions develop restricted to the solitary lymphoid follicles or lymphoid aggregates of the mucosa, especially in the ileum. The leucocyte response is lympho-plasmacytic in type and is typically accompanied by cells of the mononuclear phagocyte system, which usually have swollen eosinophilia cytoplasm often containing ingested nuclear debris and red cells (typhoid histiocytes).

During the second week, these typhoid bacilli infect the macrophages and they undergo a massive proliferation. The bacteria become localized in payer’s patches. Small bowel is swollen, congested and distended. The mesenteric lymph nodes are enlarged. Salmonella also invades the intestinal epithelial cells.

The mechanism of intestinal perforation in typhoid fever is hyperplasia and necrosis of Payer’s patches of the terminal ileum. Payer’s patches become deeply ulcerate typically forming oval, longitudinal ulcers (with the long axis along the length of the intestine)\textsuperscript{10}. Ulceration progress to capillary thrombosis and subsequent necrosis. These ulcerations are always located on the ant mesenteric border of the intestine and may perforate, usually in 3rd week of disease.\textsuperscript{10} The gut in typhoid fever is edematous and friable (especially last 60 cms). There may be one or several perforations and many other impending perforations, which makes the surgery difficult.\textsuperscript{1}

An increase in titer of agglutinins against the somatic (O) and flagellar (H) antigens of S typhi occurs (basis for Widal test). Histopathologically the ulcerated area in intestine show macrophages containing engulfed nuclear debris along with RBCs (erythrophagocytosis). Lymphocytes and plasma cells are also present (Fig). Neutrophils are spares, except near the ulcerated surface. Bloody diarrhea occurs during this phase. The commonest complications of a typhoid ulcer are hemorrhage and perforation with peritonitis.

The bacteria disseminates throughout the body via the blood vessels and lymphatics. Liver shows areas of necrosis and typhoid nodules (aggregates of macrophages). The spleen is enlarged and soft with prominent phagocyte hyperplasia.

The median age group in our study was 47 years with a range of 21-67 years and 37.5 % fell in the 40-50 years range which was similar to the age group in other studies. Abdullah et al reported average age of 42 years in their study of 82 patients with Ileal perforation.\textsuperscript{3} This age parallels the prevalence of typhoid fever which is commonly seen in this age group. The male to female ratio in our study was 4.33:1. Shrivastava D et al. in their study showed a male to female ratio of 6.38:1 similar to our results. Ileal perforation is predominantly seen in male patients.

Clinical manifestations start with bacteremia, high-grade fever, signs of systemic sepsis with characteristic normal or low blood counts and anemia. Pain abdomen as a symptom is most common in cases of perforation and was seen in 100 % of our cases. This was also shown in studies by Khalid S et al.\textsuperscript{4} In their study of 125 cases and reported pain abdomen in 100% of patients. Air under diaphragm was seen in 87.5% of our cases, similar results were obtained by Babu RG et al.\textsuperscript{11} Found pneumoperitoneum in 96.35% of their patients.

The clinical features in our study were similar to any other acute abdominal condition. The decision for a laparotomy was mainly clinical supplemented by investigations. However no single investigation was specific. The delay in operation since the estimated time of perforation was mainly prehospital. This is due to the fact that there most of the cases came from remote areas where the medical facilities are scarce.

The need for aggressive fluid resuscitation and correction of electrolyte derangements and anemia; suitable antibiotic combination is crucial to surgical outcomes. Typhi is very sensitive to antimicrobial agents. The timing of antimicrobial therapy could be critical in preventing serious complications such as perforation.\textsuperscript{7} The antibiotic protocol is to cover for not only the Salmonella organism but also for anaerobes and gram-negative coliforms. The emergence of chloramphenicol resistant, Salmonellae, has led to the use fluoroquinolones (for example, ciprofloxacin), or third generation cephalosporins.\textsuperscript{5} Enteric perforation being extremely rare in developed countries during the era of
antibiotic use supports the early use of effective antibiotics in patients with typhoid fever. In this study we have used piperclillin with tazobactum, metrogyl and amikacin.

Prompt surgery after adequate resuscitation, is the treatment of choice for typhoid perforation; this has considerably reduced mortality from 30-60% to approximately 6.8% in a recent series.12,13 The presence of single ileal perforations in majority 74.58% of our patients is consistent with other reports. All of our patients were operated under general anesthesia. Simple debridement and repair of perforation is shown to be effective. Operative procedures carried out were, namely, repair and resection and anastomosis. The classical disposition of the typhoid perforation in the longitudinal axis of the ileum and on the antimesenteric border with an antecedent history of prolonged febrile illness who did not respond to antimarial, is enough to make a conclusion as to the etiology of the perforation.

To be certain that the perforation on the ileum is due to typhoid enteritis, a positive blood, stool or urine culture is necessary. However, the yield for blood culture in a patient with typhoid intestinal perforation is low, ranging from 3-34%.14 Higher yields of the Salmonella organism is obtained from cultures of the perforation edges, bone marrow, or peritoneal aspirates. Even when they are done the results do not significantly alter the operative treatment given to the patient.

Typhoid ileal perforations were seen in 92.19% in our series while it was seen in 65.60% as in the study of Sadaf et al.4

Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: a systematic literature review by Vital Mogasale states four important global public health implications.6

First, typhoid intestinal perforation CFR is high even today in Africa and Asia, alerting to the importance of typhoid prevention and control activities in those regions.

Second, to reduce typhoid intestinal perforation burden by improving access to care, aggressive resuscitation, better surgical facilities and use of appropriate antibiotics.

Third longer hospital stays are associated higher treatment costs, and greater loss of productivity. Warrants prevention activities in some regions where even if incidence is not that high.

Fourth, it provides some basic information needed for estimating disease and economic burden of typhoid in developing countries.6

In this histopathology reports Nonspecific inflammation of the terminal ileum was another predominant cause. In such cases, the operative findings were similar to that of typhoid fever but no laboratory evidence of the disease was found. Thin layer of necrotic fibrinous purulent exudate covers histopathology report revealed the ulcer base. Beneath this is a zone of infiltrate consisting chiefly of neutrophils, below this is a zone of granulation tissue formation hich is infiltrated by lymphocyte histiocyes. Fibrocollagenous scar is seen deeper to the granulation tissue.

Abdominal tuberculosis constitutes a significant %age (10%) of all cases attending the emergency with an acute abdomen.7 Abdominal Tuberculosis with an acute abdomen presents as an enormous challenge to the surgeon. clinical judgment and surgical acumen to determine the extent of surgical management in an unprepared compromisated patient in the emergency setting is needed.

The initial clinical presentations are nonspecific. Commonest pathological change found are the presence of intestinal stricture, often multiple in number with or without presence of perforation situated proximally. In our study two patients had a structure just distal to their perforation (3.125%), two had tubercles studded on the mesentery and the surface of the bowel (3.125%) and one had extensive adhesions between the bowel loops (1.56%) along with the perforation.

The surgeon has to collect sufficient pathological tissue for histopathology and microbiology to overcome the diagnostic dilemma. The choice of surgical procedure depended on site and extent of disease, status of the remaining gut, general condition of the patient, surgeon’s expertise. Abdominal Tuberculosis includes tuberculosis infection of gastrointestinal tract, mesentery, lymph nodes and omentum, the peritoneum and related solid organs such as liver and spleen.8

Secondary tuberculosis usually involves the terminal ileum and cecum. Two types of lesions occur ulcerative and hyperplastic. The ulcerative type commonly affects the ileum. The lesions being in the lymphoid tissue of the intestine, the infection spreads through the lymphatics, which run in a circumferential fusion in the bowel wall. Hence, transverse ulcers are produced (i.e. with long axes perpendicular to the length of the intestine) the serosa is often studded with tubercles. The draining lymph node also shows granulomas. The ulcers heal by fibrosis with the resultant formation of transverse strictures, which cause intestinal obstruction.10 No single laboratory investigation is pathognomonic.11

Bacterial culture and tissue histopathology though confirmatory are time consuming, and immunological tests are expensive. And administration of ATT helped to treat the patients successfully. A high index of suspicion for intestinal tuberculosis is needed in patients who are on immunosuppression.9
A 9% was the rate of perforation in biopsy proven GI tract lymphomas in a study conducted by Vaidya et al. Comparing studies, higher % of perforations occurred in the small bowel. In this study there were no cases of lymphoma reported. Lymphoma of gastrointestinal tract is primary or secondary as part of systemic process. It accounts for 15-20% of all cases of NHL. Primary gastrointestinal lymphoma is very rare about 1% - 4% of all gastrointestinal malignancies. The most frequent sites of extra nodal lymphoma in order of its occurrence are - the stomach, small intestine and ileocecal region. Small intestinal lymphomas Gross appearance can be aneurysmal, ulcerative, polyploidy, or annular. The most common Diffuse Large B-cell Lymphoma. T-cell lymphoma comprises only 10-25%. Some histological subtypes have been noted to occur at particular site as Mucosa-Associated Lymphoid Tissue lymphoma (MALT) in involvement stomach, Mantle Cell Lymphoma (MCL) in terminal ileum, jejunum and colon. Microscopically DLBCL shows large cells which may be cleaved, non-cleaved or immunoblastic. It may show lineage of B-cell by being positive for B-cell antigens (CD 20, CD 22, CD 19, CD 70/A, and BSAP/PAX5) and very rarely positive for germinal centre cell markers (BCL6 and CD10). Clinical presentation nonspecific abdominal complaints (fatigue, malaise, weight loss, and abdominal pain), malabsorption, obstruction, or palpable mass. Very rarely, small intestinal lymphomas may present with perforation. Males have more tendencies to have perforation than females, perforations has poor out come and lead to wound infection, increase in duration of hospital stay, MODS, SIRS, undue delays in chemotherapy and ultimately mortality. 

Primary neoplasms of jejunum and ileum are only <2% of the gastrointestinal malignant tumors, the incidence were 1.4 per 100 000. Small bowel malignancy presenting as perforation is not common. PMTSB is a rare malignancy. Most PMTSB patients have nonspecific clinical symptoms and signs. In this series, the most frequent symptoms were abdominal pain (67.4%), abdominal mass (31.2%) and bowel obstruction (24.1%), followed by hemotochezia (21.3%), jaundice (16.3%), fever (14.2%), coexistence of bowel perforation and peritonitis (5.7%), coexistence of gastrointestinal bleeding and shock (5.0%), and intraabdominal bleeding (1.4%).

Hatzaras et al showed that carcinoid tumor is the most common intestinal cancer, followed by adenocarcinoma ileum is the most common site (44.7%), followed by jejunum (30.5%), duodenum (24.8%), and that the most prevalent histological type is adenocarcinoma (43.3%), followed by GIST (19.8%), carcinoid (12.1%), malignant lymphoma (9.9%), leiomyosarcoma (7.1%), malignant melanoma (4.3%), malignant neurilemmoma (2.1%) and fibro sarcoma (1.4%), indicating that carcinoid tumor is more frequently found in ileum than adenocarcinoma in duodenum.

Treatment of PMTSB is mainly based on its histopathological type, location and extent. If the tumor is located at jejunum or ileum, an aggressive segmental resection and primary anastomosis are indicated. If the tumor is located at ileum around the ileocolon junction, ileocolonic resection or right hemi-colectomy is indicated. En bloc resection is the principal procedure for most PMTSB patients and chemotherapy is the important treatment modality for malignant lymphoma and other small bowel malignant tumors with no indication for radical resection.

**CONCLUSION**

This study has attempted to determine the clinic pathological characteristics in ileal perforations. Terminal ileal perforation should be suspected in all cases of peritonitis especially in developing countries and surgical treatment should be optimized taking into account etiopathology. Enteric perforation is a strong possibility. Early diagnosis and treatment avoids extensive procedures and is associated with lower morbidity and mortality. Nonspecific inflammation of the terminal ileum was another predominant cause only operative findings were similar to that of typhoid ulcer. Abdominal Tuberculosis is very difficult to diagnose and diagnosis is often delayed till an acute abdomen is presented with. Irrespective of surgery, all patients of abdominal tuberculosis require a full ATT. Due to the lack of characteristic symptoms and a low incidence rate Primary intestinal lymphoma is misdiagnosed until serious complications occur, such as perforation and bleeding and hence needs to be accurately diagnosed. Primary neoplasms of the jejunum and ileum are infrequent and lack specific manifestations with coexistence of bowel perforation and peritonitis being (5.7%) and inaccessibility of conventional endoscopy, so the diagnosis of these tumors is usually delayed. While providing surgical care, the surgeon has to collect sufficient pathological tissue for histopathology and microbiology to overcome the diagnostic dilemma.

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