

# Usefulness of Histopathological Examination in Nontraumatic Perforation of Small Intestine

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## Abstract

**Introduction** Nontraumatic perforation of small intestine (NTPSI) is a fairly common cause of peritonitis in developing world requiring early surgical intervention. Various etiological factors have been proposed for the cause of small bowel perforation. This retrospective study was conducted with an aim to determine the prevalence patterns of the different etiologies of NTPSI.

**Materials and Methods** A total of 164 patients were included in the study who had segments of small intestine removed for perforation during emergency procedures. Preoperative definitive diagnoses were not known in these cases. On gross examination, most of the small intestine perforations,  $n=110$  (67%), were found in the terminal ileum. On microscopy, the most frequent category was that of ulcers of nonspecific etiology,  $n=61$  (37.2%), which showed general features like inflammatory granulation tissue, serositis, and foreign body giant cell reaction.

**Results** In cases where a definite opinion could be established, infection was the commonest cause,  $n=71$  (43.3%), wherein tuberculosis (49, 29.9%) and typhoid (22, 13.4%) constituted the greatest number of cases. There were two cases of lymphoma and one case of metastatic adenocarcinoma involving the small intestine. Thus, histopathological examination of operated specimen is a useful guide for the surgeon to decide further management of the patient especially in the case of infections.

**Keywords** Histopathology · Perforation · Small intestine

## Introduction

Intestinal perforation is a common cause of peritonitis necessitating immediate surgical intervention. Nontraumatic perforation of small intestine (NTPSI) refers to those perforations in which external trauma as an etiology has been excluded.<sup>1,2</sup> Various etiologies have been suggested for NTPSI; however, the distribution of these etiologies

across the globe is variable. This condition is seldom seen in the western world<sup>3</sup> where it is mostly attributable to foreign bodies, Crohn's disease, primary ischemic events, and as a part of systemic disorders.<sup>3–5</sup> However, in developing countries infectious conditions like typhoid and tuberculosis predominate the etiology of NTPSI.<sup>6,7</sup> The operating surgeons should thus be aware of the diverse etiologies of NTPSI, which would affect the management and hence the prognosis of the patient. In view of the significant number of intestinal segments that we receive in our department for histopathology, this study was carried out to study the prevalence patterns of the different etiologies of NTPSI.

## Materials and Methods

This retrospective study was conducted in the Department of Histopathology of our Institute during 2007–2008. Segments of small intestine excised for perforation during

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emergency procedures were included in the study. Preoperative definite diagnoses were not known in these cases. Cases in which only ulcer edge biopsies were taken were excluded. The intestinal segments were fixed in buffered formalin. Appropriate sections were taken from the ulcer edge, stricture, tubercles, and lymph nodes, if any, and embedded in paraffin. Routine hematoxylin and eosin-stained sections were available in all cases, and special stains were performed whenever required.

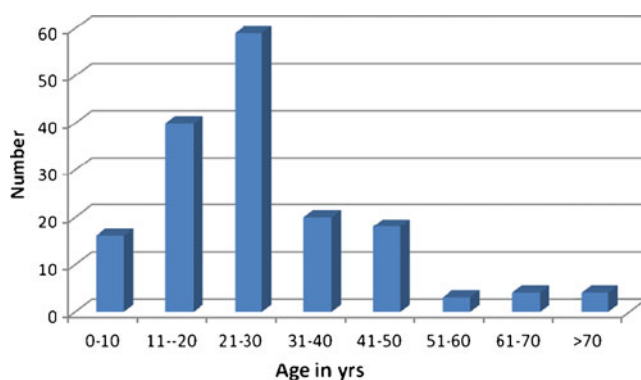
## Results

A total of 164 patients were included in the study, of which 94 were males and 70 were females, with a male/female ratio of 1.34:1. There was a wide age range, with the youngest patient being a two-and-a-half-year-old female child and the eldest being a 72 years old male (Fig. 1). The mean age of the patients was 27 years.

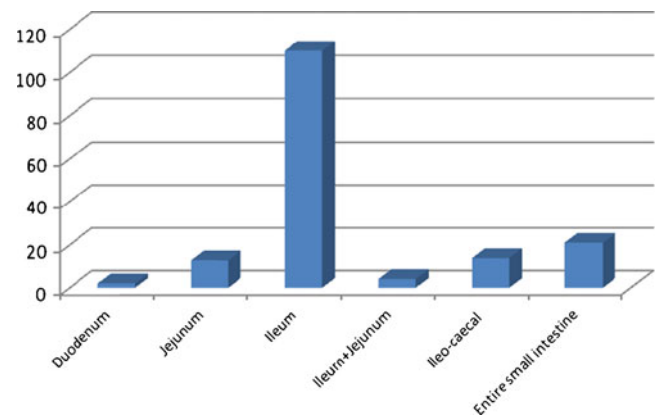
The most common presenting complaints of patients were abdominal pain, vomiting, constipation, and abdominal distension. A plain abdominal X-ray was available preoperatively in all cases and showed gas under diaphragm and multiple air fluid levels.

On performing gross naked eye examination of formalin fixed specimen, it was found that majority of the small intestine perforations, 110 (67%), were present in the terminal ileum (Fig. 2). Multiple perforations involving the ileocecal region and both ileum and jejunum were found in 25 (15%) and 14 (8.5%) cases, respectively. Isolated jejunal perforation was seen in 13 (7.9%) cases.

While 92 cases showed presence of perforation only, 36 patients had perforations along with stricture and/or ulcer. Twenty-eight patients had an ulcer accompanying the perforation, while eight cases had a stricture along with the perforation. Tubercles were found studded on serosal aspect in 13 cases, and in 35 cases, enlarged lymph nodes could be dissected out.



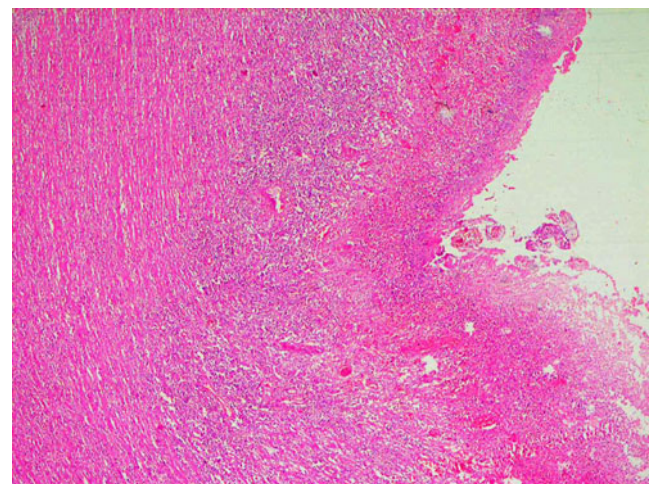
**Fig. 1** Age-wise distribution of intestine perforations



**Fig. 2** Distribution of perforations on the basis of site

Histological examination revealed that maximum number of cases ( $n=61$ ) had nonspecific features like inflammatory granulation tissue, serositis, and foreign body giant cell reaction (Fig. 3). Amongst the cases where a definitive opinion could be given, most were diagnosed as intestinal tuberculosis, followed by typhoid (Table 1).

Cases with tuberculosis showed epithelioid cell granulomas. Caseous necrosis was seen in most of these cases. All the 13 tubercles which were examined showed granulomatous inflammation, some showing caseous necrosis too (Fig. 4). Segments with typhoid perforation showed erythrophagocytosis in the region of ulcer associated with histiocytic granulomas (Fig. 5). Ischemic necrosis of variable extent was seen in the intestinal segments involved by gangrene. Strangulated hernias and volvulus were diagnosed grossly and showed similar findings. Perforation due to worms (*Ascaris lumbricoides*) and Meckel's diverticula were also gross diagnoses. Incidentally, one of the two patients with worms showed epithelioid cell granulomas with necrosis and the other showed erythropha-



**Fig. 3** Section from nonspecific ulceration showing denuded mucosa lined by inflammatory granulation tissue. H&E  $\times 40$

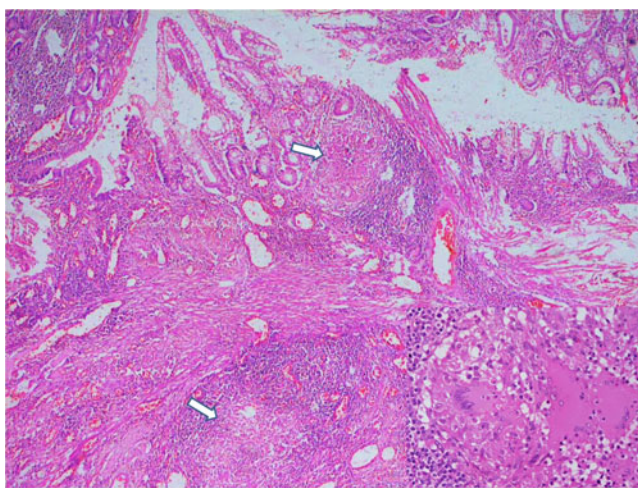
**Table 1** Etiology of small intestine perforations

Diagnosis	No. of cases (%)
Nonspecific features	61 (37.2)
Tuberculosis	49 (29.9)
Typhoid	22 (13.4)
Gangrene	17 (10.4)
Strangulated hernia	3 (1.8)
Meckel’s diverticular perforation	4 (2.4)
Volvulus	3 (1.8)
Worms	2 (1.2)
NHL	2 (1.2)
Adenocarcinoma	1 (0.6)

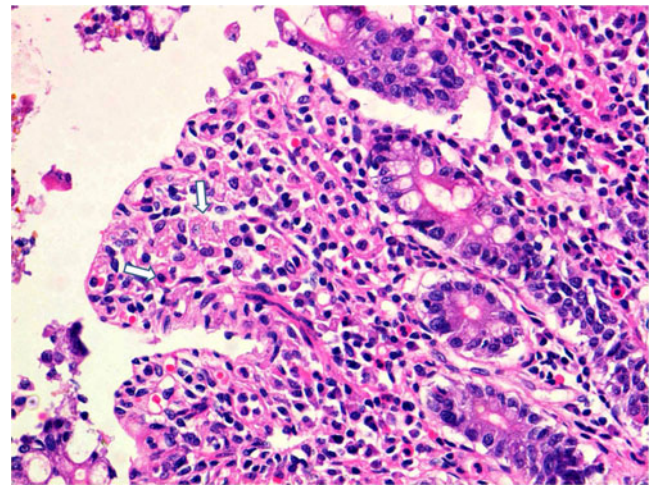
gocytosis, indicative of tuberculosis and typhoid respectively, suggesting worms as coincidental findings

There were two cases of non-Hodgkin lymphoma involving small intestine. Both showed a monomorphic lymphoid cell population of small to medium sized cells involving the layers of intestine (Fig. 6). Lymphoepithelial lesion was seen in one of them. There was only one case of metastatic adenocarcinoma, showing irregularly shaped glands of variable sizes and highly pleomorphic cells infiltrating the wall of intestine from serosal aspect.

In all the cases with lymph nodes examined, the findings in the lymph nodes supplemented those of the intestinal segment. Only in two of the 35 cases, histopathology of lymph nodes clinched the diagnosis even though the intestinal segment showed nonspecific features. In these cases, there was erythrophagocytosis in the lymph nodes which favored a diagnosis of typhoid even though no such features were seen in the intestinal segment.



**Fig. 4** Section from tuberculosis intestine with numerous epithelioid cell granulomas with giant cells and necrosis (arrows). Inset shows a higher power view of epithelioid cell granuloma and Langhans’ giant cells. H&E ×40

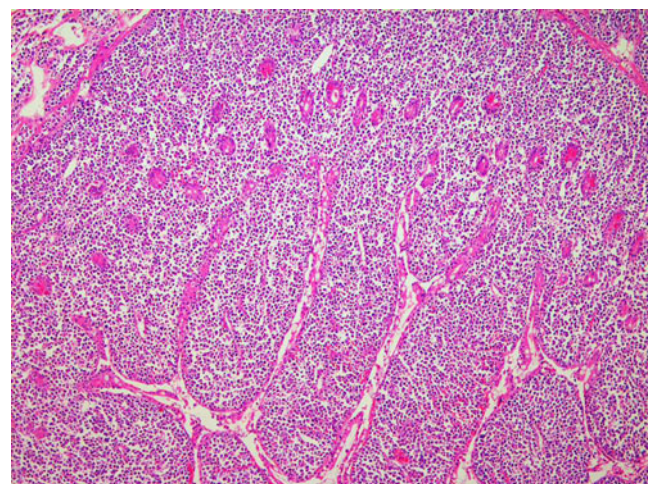


**Fig. 5** Section from typhoid ulcer shows lymphoid hyperplasia with clusters of erythrophagocytic histiocytes (inset, arrow). H&E ×400

**Discussion**

A wide range of etiological factors have been proposed for the causation of small bowel perforation. Knowledge of the possible etiologic factors is of great importance to the surgeon as a guide to adapting the operative procedure for the intestinal lesion.

Nontraumatic perforation of the small intestine is a rare entity in the western literature.<sup>3</sup> However, with the large number of cases diagnosed every year, NTPSI appears to be fairly common in the tropics.<sup>8,9</sup> In the present study, most of the patients were in the age group of 21–30 years which is in contrast to studies in the western countries where it primarily occurs in the elderly.<sup>3</sup> This may be explained by the difference in the settings in which these perforations occur. The western literature suggests that foreign body,



**Fig. 6** Section showing mucosa, submucosa, and muscularis propria infiltrated by monomorphic lymphoid population in non-Hodgkin lymphoma. H&E ×100

ischemia, radiotherapy, diverticula, Crohn's disease, etc. are the main causes of perforation, which are more commonly seen in elderly patients.<sup>5</sup> In contrast to this, infection is the commonest cause of such perforations in developing countries. This includes typhoid fever and tuberculosis which are quite common in young.<sup>5,6,10</sup> The findings in the present study are consistent with this trend; as in 71 (43.3%) cases, an infectious etiology, either due to tuberculosis or typhoid, could be established.

Despite considerable progress made in therapy and prophylaxis, abdominal tuberculosis is still common in developing countries<sup>11</sup> and its incidence is increasing in the western world too.<sup>12</sup> Although perforation due to abdominal tuberculosis is supposed to be uncommon because of reactive thickening of the peritoneum and formation of adhesions with surrounding tissues,<sup>13</sup> it is still a serious complication that occurs in 1–10% of all patients with abdominal tuberculosis.<sup>13,14</sup> The perforation is most commonly found in the distal ileum. Of the 49 patients, 36 patients had perforation, stricture, as well as ulcer; eight cases had a stricture along with the perforation, while five patients had only perforation. The ulcers lie transverse to the intestine axis which can be explained by the lymphatic network distribution in that area. Histopathology of the intestinal segments revealed epithelioid cell granulomas with or without caseous necrosis. The histopathology of the tubercles and the associated lymph nodes was consistent with tuberculosis in all cases. Subsequent to histopathologic diagnosis, patients were started on a standard four-drug anti-tubercular treatment (Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol) for 4 months, followed by a two-drug treatment (Isoniazid and Rifampicin) for 2 months.

Perforation, a lethal complication of typhoid fever, occurs due to necrosis of Peyer's patches in the terminal ileum, this being the most common site where the bacteria *Salmonella typhi* colonizes. Hence, the ulcers lie longitudinally along the axis of the intestine in the direction of Peyer's patches. On histopathology, erythrophagocytosis by histiocytes along with the formation of histiocytic granulomas was found in the region of the ulcer. In two cases, the intestinal segment showed nonspecific features of perforation, while the lymph node showed erythrophagocytosis. Hence, an active lookout for these can help in reaching the diagnosis in a significant number of cases.<sup>17</sup> In all cases, the diagnosis needs to be confirmed by serology and/or culture. The patients were treated with Ceftriaxone initially. Other antibiotics were given according to culture and antibiotic sensitivity.

Studies have shown that worldwide, typhoid fever is the most common cause of small intestine perforation.<sup>7,15,16</sup> In a previous study done by authors on the role of ulcer edge biopsy in diagnosing NTPSI, it was found that amongst the cases diagnosed as a definitive pathology, typhoid is the

commonest diagnosis.<sup>17</sup> However, in the present study, tubercular enteritis ( $n=49$ ) was more common than typhoid perforation ( $n=22$ ). Waisberg et al. also found similar results, wherein tuberculosis was the most frequent specific factor comprising 20.7% of the cases.<sup>18</sup> A possible explanation could be that, in case of typhoid perforation, the operative management consists of liberal peritoneal lavage with closure of perforation.<sup>10</sup> Thus, getting the entire ileal segment for histopathology is uncommon in such cases until and unless the terminal ileum is grossly inflamed with multiple perforations. On the contrary, simple closure is contraindicated in case of tuberculosis as there is always a chance of stricture, reperforation, and fistula formation. Thus resection is almost always done, which is sent for histopathological confirmation.

Next to infectious diseases, the most frequent category was that of ulcers of nonspecified etiology (37.2%). This is in concordance with studies done by Waisberg et al. wherein a specific etiology could not be found in 29.5% of the patients.<sup>18</sup> The histopathological examination of these nonspecific ulcers showed an ulcer base which was formed by granulation tissue and fibrinopurulent exudate. This was usually accompanied by foreign body giant cell reaction and serositis. In the previous study done by authors on perforation edge biopsy, it was found that typhoid and tuberculosis were the main causes in which etiology could be established on histopathology.<sup>17</sup> However, in majority of cases, no etiologic factor was apparent on biopsy specimen and those were reported as ulcers of nonspecific etiology. The patients were given a course of antibiotics in the postoperative period according to culture and sensitivity reports, and were advised follow up in outpatient department.

Strangulation in external hernia and mesenteric ischemia are known to cause small intestine perforation.<sup>5</sup> There were 17 cases of gangrene due to mesenteric ischemia and three cases due to strangulation of inguinal hernias. In both the conditions, there was widespread ischemic necrosis of the intestine. Perforation as a complication is a rare event in jejunoileal diverticula.<sup>19</sup> Leijonmarck et al. found only three cases of perforated Meckel's diverticulum.<sup>3</sup> The etiology is probably on a hypermotility basis with symptomatic patients showing active but uncoordinated peristalsis.<sup>20</sup> In three patients, the perforation was due to small bowel volvulus.

In two patients, the intestines were packed with worms, along with presence of perforation preoperatively. Interestingly, there was one patient with coincidental tuberculosis with worms and one with typhoid perforation with worms. Thus the presence of worms was a coincidental finding and not a main cause of perforation.

Lymphomas, sarcomas, and adenocarcinomas are susceptible to intestine perforation<sup>21</sup> probably due to chemo-

therapy or inadequate blood supply.<sup>22</sup> Chaikof et al., in their study, found 17 perforation cases caused by malignancy, of which 12 were metastatic.<sup>23</sup> In our study, we found only one patient with metastatic adenocarcinoma and two patients with non-Hodgkin's lymphoma. All the patients were referred to the Oncology department for further management.

While reviewing the literature, we did not encounter any study based on histologic review of small bowel perforation. In this study, we found that nontraumatic perforation in developing countries can be due to typhoid, tuberculosis, and few cases of malignancy. Even though a significant number of specimens may be nondiagnostic, histopathological examination of operated specimen definitely helps the surgeon in further management of the patient. This is particularly important in case where the etiology is infectious like tuberculosis or typhoid.

In conclusion, diagnosis of nontraumatic perforation is a challenge preoperatively. Clinical findings are usually nonspecific and definite diagnosis can be reached after histopathology. Although specimen examination is an important factor for proper management, histopathological examinations are not always informative.

**Conflicts of interest** No conflict of interest. No financial support of any form has been taken from any agency for this study.

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