Multicenter epidemiological survey of pneumatosis intestinalis in Japan

Naoki Ohmiya1*, Ichiro Hirata1, Hirotugu Sakamoto1, Toshifumi Morishita1, Eiko Saito4, Katsuyoshi Matsuoka5, Tadanobu Nagaya6, Shinji Nagata7, Miyuki Mukae13, Koji Sano9, Takayoshi Suzuki10, Ken-ichi Tarumi11, Seiji Shimizu12, Kousaku Kawashima13, Toshifumi Hibi14 and Intractable Diseases, the Health and Labour Sciences Research Group

Abstract

Background: Pneumatosis intestinalis (PI) is a rare condition characterized by gas collection in the intestinal wall. We aimed to determine the etiology and affected segments associated with complications, treatment, and outcome.

Methods: We conducted a multicenter epidemiological survey using a standardized data collection sheet in Japan. Complicating PI was defined as strangulation or bowel necrosis, bowel obstruction, adynamic ileus, sepsis, shock, and massive gastrointestinal bleeding requiring blood transfusion.

Results: We enrolled 167 patients from 48 facilities. Multivariate analysis revealed that older age (adjusted OR, 1.05 and 95% confidence intervals [CI], 1.02–1.09, P = 0.0053) and chronic kidney disease (adjusted OR, 13.19 and 95% CI 1.04–167.62, P = 0.0468) were independent predictors of the small-bowel-involved type. Complicating PI was associated with the small-bowel-involved combined type (adjusted OR, 27.02 and 95% CI 4.80–152.01, P = 0.0002), the small-bowel-only type (adjusted OR, 3.94 and 95% CI 1.02–15.27, P = 0.0472), and symptomatic PI (adjusted OR, 16.24 and 95% CI 1.82–145.24, P = 0.0126). Oxygen therapy was performed in patients with a past history of bowel obstruction (adjusted OR, 13.77 and 95% CI 1.31–144.56, P = 0.0288) and surgery was performed in patients with complicating PI (adjusted OR, 8.93 and 95% CI 1.10–72.78, P = 0.0408). Antihypertensives (adjusted OR, 12.28 and 95% CI 1.07–140.79, P = 0.0439) and complicating PI (adjusted OR, 11.77 and 95% CI 1.053–131.526; P = 0.0453) were associated with exacerbation of PI. The complicating PI was the only indicator of death (adjusted OR, 14.40 and 95% CI 1.09–189.48, P = 0.0425).

Discussion: Small-bowel-involved type and symptomatic PI were associated with complications which were indicators of poor prognosis.

Keywords: Pneumatosis intestinalis, Small bowel, Complications, Poor prognosis

Introduction

Pneumatosis intestinalis (PI) is a rare condition characterized by the collection of gas, which can have a hydrogen content up to 50%, in the intestinal wall [1, 2]. PI has been classified pathogenically into four categories: bowel necrosis, mucosal disruption, increased mucosal permeability, and pulmonary disease [2]. The relevant literature from Japan has described 12 patients with PI due to chronic occupational exposure to trichloroethylene.
Patients and methods
Study design
This was a retrospective multicenter epidemiologic study using a standardized data collection sheet. The diagnosis of PI was made with the identification of characteristic features or gas in the bowel wall by endoscopy, endoscopic ultrasonography, CT, plain abdominal roentgenogram, barium enema roentgenogram, or laparotomy. The aim of this study was to define the clinical features leading to complications and poor prognosis. Complicating PI was defined as having strangulation or bowel necrosis, bowel obstruction, adynamic ileus without mechanical obstruction, sepsis, shock, and massive gastrointestinal bleeding requiring blood transfusion. Benign PI was defined as not having those complications.

Results
Clinical characteristics of pneumatosi intestinalis
Standardized data collection sheets were returned from 48 facilities (32%) including 16 secondary and 32 tertiary health care hospitals, and 167 cases were enrolled. The patients’ demographics, comorbidities, past medical histories, and medications used are shown in Table 1. Symptoms, complications, segments involved, diagnostic examinations, treatment, outcome of PI, and prognosis are shown in Table 2.

Segment of bowel involved
A comparison of clinical characteristics between the large-bowel-only type and the small-bowel-involved type...
Table 1 Clinical characteristics of patients with pneumatosis intestinalis

| Characteristics                        | n   | (%) |
|----------------------------------------|-----|-----|
| No patients                            | 167 |     |
| Men/women                              | 87/80 |    |
| Median age of onset (years)            | 65 (range 9–91) | |
| Exposure to organic solvents           | 2 (1) |    |
| Comorbidities and/or past medical history | 141 (84) |   |
| Gastroduodenal diseases                | 45 (27) |   |
| Inflammatory bowel disease             | 16 (10) |   |
| Ulcerative colitis                     | 13 (8) |    |
| Crohn’s disease                        | 2 (1) |     |
| Behcet’s disease                       | 1 (1) |     |
| Carcinoma                              | 13 (8) |   |
| Esophageal carcinoma                   | 1 (1) |     |
| Gastric carcinoma                      | 3 (2) |     |
| Colorectal carcinoma                   | 9 (5) |     |
| Colorectal poly                        | 6 (4) |     |
| Bowel obstruction                      | 3 (2) |     |
| Others                                 | 5 (3) |     |
| Diabetes mellitus                      | 31 (19) |    |
| Chronic lung disease                   | 28 (17) |   |
| Autoimmune disease                     | 30 (18) |   |
| Hypertension                           | 13 (8) |    |
| Heart disease                          | 11 (7) |    |
| Hepatobiliary-pancreatic disease       | 10 (6) |    |
| Kidney disease                         | 4 (2) |     |
| Others                                 | 41 (25) |   |
| Medications used                       | 137 (82) |  |
| Corticosteroid                         | 45 (27) |   |
| Antidiabetics                          | 29 (17) |   |
| α-glucosidase inhibitors               | 23 (14) |   |
| Others                                 | 14 (8) |    |
| Gastric acid secretion inhibitors      | 20 (12) |   |
| Proton pump inhibitors                 | 15 (9) |    |
| Histamine-2 receptor antagonists       | 6 (4) |     |
| Antihypertensives                      | 19 (11) |   |
| Calcium antagonist                     | 10 (6) |     |
| β-blocker                              | 8 (5) |     |
| Angiotensin II receptor blocker         | 9 (5) |     |
| Angiotensin converting enzyme inhibitor| 1 (1) |     |
| α-blocker                              | 1 (1) |     |
| Immunosuppressants                     | 16 (10) |    |
| S-aminosalicylates or salicylazosulfapyridine | 15 (9) |   |
| Statins/ezetimib/fibrates              | 14 (8) |    |
| Antithrombotics                        | 12 (7) |    |
| Anticoagulants                         | 4 (2) |     |
| Antiplatelets                          | 9 (5) |     |
| Laxatives*                             | 10 (6) |    |
| Anti-cancer agents                     | 9 (5) |     |
| Herbal medicine                        | 7 (4) |     |
| Allopurinol/benzbromaron               | 3 (2) |     |
| Others                                 | 44 (26) |   |

*Magnesium oxide (n = 7); sennoside (n = 4), and sodium picosulfate (n = 4)

is shown in Additional file 2: Supplementary Table 2. Although univariate analysis demonstrated that older age, non-use of α-glucosidase inhibitors, 5-aminosalicylates, salicylazosulfapyridine, or statins/ezetimib/fibrates, negativity for ulcerative colitis, positivity for autoimmune disease, chronic kidney disease, and cancer other than that of the digestive or hematologic system were associated with the small-bowel-involved type, multivariate analysis revealed that older age (adjusted OR, 1.05 and 95% confidence intervals [CI], 1.02–1.09, P = 0.0053) and chronic kidney disease (adjusted OR, 13.19 and 95% CI 1.04–167.62, P = 0.0468) were the only independent predictors (Table 3).

Complicating pneumatosis intestinalis

A comparison of clinical characteristics between benign and complicating PI is shown in Additional file 3: Supplementary Table 3. Symptoms of complicating PI included abdominal pain/distention (n = 25, 96%) and bloody stool (n = 4, 15%) except one asymptomatic patient with hydrocephalus after subarachnoid hemorrhage, while those of benign PI included abdominal pain/distention (n = 49, 35%), diarrhea (n = 17, 12%), constipation (n = 10, 7%), and bloody stool (n = 8, 6%). The multivariate analysis revealed that the small-bowel-involved combined type (adjusted OR, 27.02 and 95% CI 4.80–152.01, P = 0.0002), symptomatic PI (adjusted OR, 16.24 and 95% CI 1.82–145.24, P = 0.0126), and the small-bowel-only type (adjusted OR, 3.94 and 95% CI 1.02–15.27, P = 0.0472) were the only independent predictors (Table 3).

Treatment of pneumatosis intestinalis

The comparison of clinical characteristics in terms of medical treatment, oxygen therapy, endoscopic therapy, and surgery is shown in Additional file 4: Supplementary Table 4. The rates of improvement, exacerbation, recurrence, and death stratified by conservative, oxygen, and surgical treatment were 67.5%, 4.3%, 0.0%, and 5.1%; 80.0%, 2.9%, 2.9%, and 2.9%; and 83.3%, 8.3%, 0.0%, and 8.3%, respectively. Univariate analysis demonstrated the following: non-use of 5-aminosalicylates/salicylazosulfapyridine, a past history of bowel obstruction, autoimmune disease, affected segments other than the large bowel associated with oxygen treatment, use of anticancer agents, the small-bowel-only type and complicating PI associated with surgery. Multivariate analysis demonstrated that oxygen therapy was performed in patients with a past history of bowel obstruction (adjusted OR, 27.02 and 95% CI 4.80–152.01, P = 0.0002), symptomatic PI (adjusted OR, 16.24 and 95% CI 1.82–145.24, P = 0.0126), and the small-bowel-only type (adjusted OR, 3.94 and 95% CI 1.02–15.27, P = 0.0472) were the only independent predictors (Table 3).
Outcome of pneumatosis intestinalis

The comparison of the clinical characteristics among the outcomes of PI, namely, improvement, no change, and exacerbation, is shown in Additional file 5: Supplementary Table 5. Univariate analysis demonstrated that non-use of α-glucosidase inhibitors and use of 5-aminosalicylates/salicylazosulfapyridine associated with no change, use of antihypertensives, chronic kidney disease, and involved segments other than the large bowel were associated with exacerbation. Multivariate analysis demonstrated that the use of antihypertensives (adjusted OR, 12.28 and 95% CI 1.07–140.79, \( P = 0.0439 \)) and complicating PI (adjusted OR, 11.77 and 95% CI 1.053–131.526; \( P = 0.0453 \)) were associated with exacerbation of PI, as shown in Table 3.

Death associated with pneumatosis intestinalis

The comparison of clinical characteristics in terms of survival and death associated with PI is shown in Additional file 6: Supplementary Table 6. Although the univariate analysis demonstrated that the use of α-blocker, laxatives, cirrhosis, and chronic kidney disease, the small-bowel-involved type, complicating PI were associated with death, the multivariate analysis revealed that the complicating PI was the only indicator of death (adjusted OR, 12.28 and 95% CI 1.07–140.79, \( P = 0.0439 \)) and complicating PI (adjusted OR, 11.77 and 95% CI 1.053–131.526; \( P = 0.0453 \)) were associated with exacerbation of PI, as shown in Table 3. Of the eight patients, 6 died from complicating PI (4 with bowel infarction, 1 with septic shock, and 1 with massive gastrointestinal bleeding), and 2 died from severe comorbidities such as liver cirrhosis with chronic kidney disease and acute leukemia followed by graft-versus-host disease.
Discussion

The present multicenter epidemiologic study demonstrated that complicating PI, such as strangulation or bowel necrosis, bowel obstruction, adynamic ileus, sepsis, shock, and massive gastrointestinal bleeding, was significantly associated with the small-bowel-involved combined type, the small-bowel-only type, and symptomatic PI. These results support the findings of another prospective multicenter study including 127 PI patients sponsored by the Association for Surgery of Trauma: the small bowel location of PI, peritonitis, and abnormal laboratory values such as an elevated international normalized ratio, decreased hemoglobin, and lactate values greater than 2.0 mmol/L were predictive of pathologic PI defined as the presence of transmural ischemia during surgical exploration or autopsy [8]. Similarly, the largest-scale retrospective multicenter epidemiologic study of the Eastern Association for the Surgery of Trauma including 500 patients demonstrated that the large bowel disease was the most common site for PI, but the jejunal and ileal pneumatosis locations were most commonly associated with pathologic PI [6]. A retrospective single-center study including 70 patients with PI or portal vein gas-clarified acute mesenteric ischemia was associated with small bowel PI, abdominal pain, elevated lactate, and the calculated vascular disease score [9]. These studies are in line with the present finding, but in a retrospective single-center study including 97 patients with PI (46% colon, 27% stomach, 5% stomach, and 7% both small and large bowel), Morris et al. reported that the location of pneumatosis alone was not predictive of outcome or intervention [10]. The present study has the inherent limitation of its lack of data on blood and physical findings, but a comprehensive diagnosis that includes a physical examination with parameters such as vital and peritoneal signs, laboratory tests, and imaging modalities, is essential to rule out complicating PI. This small-bowel-involved type was shown to be significantly associated with older age and chronic kidney disease in the present study. Among the four cases with chronic kidney disease, 3 were the small-bowel-only type while 1 was the large-bowel-only type, the difference of which seems marginal with P-values of 0.0468. There have been no reports regarding the association between affected segments of PI and kidney disease, but DuBose et al. described that patients with pathologic type were more likely to be older, with a history of enteritis and chronic renal failure [6]. Chronic kidney disease, especially end-stage renal disease increased

| Table 3 | Multivariate analysis of segments, complications, treatment, and outcomes of pneumatosis intestinalis |
|---------|--------------------------------------------------------------------------------------------------|
| Characteristics | Adjusted OR | 95% CI | P |
| Segment of bowel involved | | | |
| Small‑bowel‑involved type | | | |
| Age | 1.05 | (1.02–1.09) | 0.0053 |
| Chronic kidney disease | 13.19 | (1.04–1.67.62) | 0.0468 |
| a‑glucosidase inhibitors | 0.27 | (0.07–1.01) | 0.0519 |
| Complicating pneumatosis intestinalis | | | |
| Small‑bowel‑involved combined type | 27.02 | (4.80–152.01) | 0.0002 |
| Symptomatic | 16.24 | (1.82–145.24) | 0.0126 |
| Small‑bowel‑only type | 3.94 | (1.02–15.27) | 0.0472 |
| Treatment | | | |
| Oxygen therapy | | | |
| Past history of bowel obstruction | 13.77 | (1.31–144.55) | 0.0288 |
| Proton pump inhibitors | 3.14 | (0.83–11.96) | 0.0928 |
| Surgery | | | |
| Complicating pneumatosis intestinalis | 8.93 | (1.10–72.78) | 0.0408 |
| Small bowel only segment | 6.21 | (0.74–52.18) | 0.9260 |
| Outcomes of pneumatosis intestinalis | | | |
| Exacerbation | | | |
| Antihypertensives | 12.28 | (1.07–140.79) | 0.0439 |
| Complicating pneumatosis intestinalis | 11.77 | (1.053–131.526) | 0.0453 |
| Prognosis of patients with pneumatosis intestinalis (death) | | | |
| Complicating pneumatosis intestinalis | 14.40 | (1.09–189.48) | 0.0425 |

Bold indicate P-values less than 0.05
intestinal permeability[11], which might be associated with PI affecting both the small and large bowels. In contrast to the large-bowel-only type associated with a-glucosidase inhibitors and ulcerative colitis, the small-bowel-involved type associated with older age, autoimmune disease, chronic kidney disease, and cancer can be more intractable and vulnerable to blood perfusion, which leads to the speculation of this type more complicating.

Regarding treatment, oxygen therapy was significantly associated with patients with a past medical history of bowel obstruction, and surgery was significantly associated with complicating PI. Hyperbaric oxygen therapy is a controversial treatment for adhesive postoperative small bowel obstruction, but Fukami et al. described that 143 patients (87.7%) were treated successfully with hyperbaric oxygen therapy without long-tube decompression. This oxygen therapy was associated with earlier resumption of oral intake and a shorter hospital stay, and the rate of operation was 7.4% in the hyperbaric oxygen therapy group and 14.8% in group treated by decompression alone [12]. In this context, patients with PI with a history of bowel obstruction likely underwent oxygen therapy. Duron et al. reported that abdominal distention, peritonitis, and lactic acidemia were predictive of positive intraoperative findings mandating intervention including mesenteric ischemia, an obstruction, or an incarcerated hernia on multivariate analysis in a retrospective multicenter record review of 150 PI patients, 54 (36%) of whom were managed nonoperatively, 72 of whom underwent surgery, and 24 of whom were given comfort measures only [13]. Generally, complicating or pathologic PI is an indication for surgery, as shown in the present study.

The last finding of the present study was that complicating PI was significantly associated with exacerbation of PI and subsequent death, which also makes medical sense. Wiesner et al. reported that of seven patients with infarction limited to one bowel segment (jejunum, ileum, or colon), only one patient (14%) died, whereas of the 10 patients with infarction of two or three bowel segments, eight patients (80%) died. These authors concluded that CT findings of PI and portomesenteric venous gas due to bowel ischemia do not generally allow prediction of transmural bowel infarction because these findings may be observed in patients with only partial ischemic bowel wall damage, and the clinical outcomes of patients with bowel ischemia with these CT findings seem to depend mainly on the severity and extent of their underlying disease [14], which is consistent with our comprehensive finding.

The present study has inherent limitations, including its retrospective design, ethnically homogeneous sample, low response rate to this survey, no laboratory data or images included, no CKD classification obtained, and participation bias in terms of data collection, which was conducted mainly by gastroenterologists and a few surgeons but no radiologists or acute care physicians. Therefore, the proportion of surgery in the treatment was as low as 4.6%.

Conclusions

In conclusion, our study highlights that small-bowel-involved type and symptomatic PI are associated with complications which are indicators of poor prognosis in the largest Asian population ever.

Abbreviation

PI: Pneumatosis intestinalis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-022-02343-5.

Additional file 1. Supplementary Table 1.
Additional file 2. Supplementary Table 2.
Additional file 3. Supplementary Table 3.
Additional file 4. Supplementary Table 4.
Additional file 5. Supplementary Table 5.
Additional file 6. Supplementary Table 6.

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Intractable Diseases, the Health and Labour Sciences Research Group Naoki Ohmiya1, Ichiro Hirata1, Hirotugu Sakamoto1, Toshifumi Morishita2, Eiko Satō2, Katsuyoshi Matsuoka2, Tadanobu Nagaya2, Shinji Nagata2, Miyuki Mukae2, Koji Sano2, Takayoshi Suzuki2, Ken-ichi Tarumi2, Seiji Shimizu3, Kousaku Kawashima3, Toshifumi Hib4, Akimichi Imamura5, Yohei Minato5, Kazuhiro Matsueda6, Go Kuvata6, Masahiro Sakaguchi7, Daishi Saito7, Sakae Mikami7, Mitsuhito Fujishiro7, Shigeihiko Fuji7, Junji Umeno7, Kenji Aoi2, Daishi Nishihara2, Fukunori Kinjo5, Mizukazu Fujisa5, Keita Harada6, Mitsunobu Matsushita7, Toshimi Chiba2, Tatsuya Sakai3, Shinji Tanaka3, Yoshiaki Asami9, Kunio Kasugai10, Shojiro Yamamoto10, Nobuaki Yagi11, Tomoo Yosie12, Masaki Yoshida12, Shin Fukudo12, Takanori Yamada13, Kousuke Kitsugi14, Shigeru Kuriyama14, Soichiro Miura15, Yoshiya Fujimoto15, Yasumasa Niwa14, Takashi Nishikawa16, Kyotaka Okawa16, Makoto Sanomura17, Masanao Nakamura18, Tsutomu Mizoshita19, 1 Departments of Gastroenterology and Advanced Endoscopy, Fuji Health University School of Medicine, 1-98 Kutsukake-cho, Toyoka, Aichi 470-1192, Japan; 2Department of Medicine, Division of Gastroenterology, Ichi Medical University, Tochigi, Japan; 3Division of Gastroenterology, Matsuyama Red Cross Hospital, Matsuyama, Japan; 4Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan; 5Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan; 6Department of Gastroenterology, Shinshu University School of Medicine, Matsumoto, Nagano, Japan; 7Department of Gastroenterology, Hiroshima City Asa Citizens Hospital, Hiroshima, Japan; 8Department of Gastroenterology, Kitasato University, School of Medicine, Kanagawa, Japan; 9Department of Gastroenterology, Osaka City General Hospital, Osaka, Japan; 10Department of Gastroenterology, Tokyo University School of Medicine, Kanagawa, Japan; 11Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School, Kurashiki, Okayama, Japan; 12Departments of Gastroenterology and Hepatology, Osaka General Hospital of West Japan Railway Company,
Declarations

Ethical approval and consent to participate
This study was reviewed and approved by the institutional review board and ethics committee of Fujita Health University Hospital (ID: HM20-253), and in accordance with the guidelines of national/international/institutional or Declaration of Helsinki. Informed consent was obtained in the form of opt-out on the web-site. Those who rejected it were excluded. All authors had access to the study data and reviewed and approved the final manuscript.

Consent for publication
Not applicable.

Competing interests
We disclose no reports or publications that contain any materials that appear in the article. The authors have no conflicts of interest to declare including employment, consultancies, honoraria, stock ownership and options, expert testimony, grants or patents received or pending, royalties which took place in the previous three years.

Author details

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