Original Article

Clinical characteristics and prediction of the asymptomatic phenotype of pneumatosis intestinalis in critically ill patients: a retrospective observational study

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Aim: The differences in clinical characteristics between benign asymptomatic and symptomatic pneumatosis intestinalis (PI) remain unknown. This study aimed to reveal the clinical characteristics of PI in critically ill patients.

Methods: This was a retrospective observational study undertaken between 2013 and 2017 in a single facility. Patients with PI were enrolled. Pneumatosis intestinalis was diagnosed using computed tomography, and clinical data were collected. Pathologic PI refers to PI with bowel ischemia. Asymptomatic PI refers to PI with a benign etiology.

Results: There were 17 patients with pathologic PI and 31 with asymptomatic PI. Pathologic PI was detected at day 4 of hospital stay, and asymptomatic PI was detected at day 30 of hospital stay ($P < 0.01$). The symptoms that were different between pathologic and asymptomatic PI were acute diarrhea (18% and 65%, $P = 0.01$), C-reactive protein level elevation (9.9 and 2.1 mg/dL, $P = 0.01$), and systemic inflammatory reaction syndrome (100% and 13%, $P < 0.01$). Computed tomography findings showed a difference in the occurrence of ascites collection (94% versus 23%, $P < 0.01$) and PI of the ascending colon (47% versus 80%, $P = 0.02$). Hospital mortality of pathologic PI was 88%, whereas all patients with benign PI survived. The positive likelihood ratio of acute diarrhea with PI of the ascending colon to diagnose benign PI was 7.33 (1.11–48.5).

Conclusions: Pneumatosis intestinalis of the ascending colon that occurs in the post-intensive care phase with a poor inflammatory reaction, acute diarrhea, and no ascites collection could be benign. In other cases, bowel ischemia should be promptly ruled out.

Key words: Acute diarrhea, ascending colon, bowel ischemia, critically ill patient, pneumatosis intestinalis

INTRODUCTION

PNEUMATOSIS INTESTINALIS (PI) refers to the presence of gas within the wall of the small intestine or colon. Although the true incidence of PI is unknown, the expanded use of computed tomography (CT) imaging could contribute to the increase in detection of this finding. The pathogenesis of PI is poorly understood and could be multifactorial. It is suggested to be related to a wide variety of pathologies.[1–10] A recent multicenter study reported that 60% of patients with PI have been reported to have benign etiology.[11] It has also been reported that most patients with PI are asymptomatic and probably never come to clinical attention,[12] suggesting that PI is an incidental finding associated with benign etiologies, whereas bowel ischemia with PI portends a life-threatening intra-abdominal condition.

Although PI in critically ill patients must be considered as a pathologic phenotype secondary to bowel ischemia, the difference in clinical characteristics between benign asymptomatic PI and life-threatening PI is still unknown.

Therefore, this study aimed to investigate the clinical characteristics of PI in critically ill patients to distinguish asymptomatic and pathologic PI.

METHODS

THIS WAS A retrospective, single institutional cohort study using patient records from the intensive care unit

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(ICU) of a university hospital. Data were collected between 1 January, 2013 and 31 December, 2017. Follow-up was finished on 31 March, 2018.

Participants

Adult patients stayed at least 3 days in the ICU, and those who were detected with PI after admission were enrolled. Pneumatosis intestinalis was diagnosed using CT scan. Diagnosis and localization of PI were carried out by staff radiologists.

Data collection

Age, sex, comorbidity of diabetes, hospital days of PI detection, and in-hospital mortality were collected.

Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores at the time of admission were also calculated to evaluate physiological severity.

At the diagnosis of PI, the occurrence of systemic inflammatory response syndrome (SIRS),[13] acute diarrhea, hematochezia, serum C-reactive protein (CRP) level elevation, lactate dehydrogenase (LDH) level elevation, creatine phosphokinase (CPK) level elevation, portal venous gas, ascites collection, and site of pneumatosis were recorded. Diagnosis and detection of portal venous gas and ascites collection were also evaluated by staff radiologists.

Computed tomography scan was carried out: (i) when the patient showed clinical, laboratory, or clinicopathologic evidence of a bowel disease with potential associated morbidity or mortality and needed invasive intervention, as previously reported;[14] or (ii) when follow-up imaging was required without targeted therapeutic intervention or no clinicopathologic or laboratory evidence of a specific underlying bowel disease. Pathologic PI was defined as the presence of transmural ischemia during surgical exploration or subsequent clinical course. Asymptomatic PI was defined as the condition with a benign etiology where no invasive procedures are indicated.

Acute diarrhea was defined as at least three to four liquid stools/day,[15] continued for more than 48 hours before PI, and needed to interrupt enteral nutrition.[16] The decision of interruption depended on each physician.

Initial diagnosis of central nervous system and cervical cord injury indicates stroke, traumatic brain injury, and cervical cord injury.

Trauma indicates multiple traumas, excluding isolated traumatic brain injury and cervical cord injury.

Digestive disease indicates bowel obstruction, severe pancreatitis, and ischemic colitis.

Sepsis was defined as infection with SIRS, and septic shock was defined as a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes, by Sepsis-2 definition.[17]

Cardiovascular disease indicated thoracic aortic dissection, post-cardiac arrest syndrome with ventricular fibrillation, and congestive heart failure.

Statistical analysis

Data are presented as median values (interquartile range) or *n* (%). The Wilcoxon signed-rank test and Fisher's exact test were applied to evaluate differences in characteristics. To evaluate the predicting ability for benign and pathologic PI, sensitivity, and specificity, positive predictive value and positive likelihood ratio were calculated. Statistical analysis was undertaken using JMP Pro version 11 (SAS Institute Japan, Tokyo, Japan), and $P < 0.05$ was considered statistically significant.

RESULTS

DURING THE STUDY period, 2,438 patients were admitted and stayed for 3 days or more. There were 48 patients with PI: 17 cases were pathologic PI, and 31 were asymptomatic (Fig. 1). The diagnosis of asymptomatic PI was made in 22 patients during investigations undertaken for non-life-threatening abdominal symptoms, and in five patients by abdominal imaging for follow-up study of the original conditions.

Characteristics of patients

Patient characteristics are shown in Table 1. Presence of preexisting diabetes and admission conditions differed between groups. The clinical status at the time of PI detection is shown in Table 2. Asymptomatic patients were diagnosed with PI later than pathologic patients. Different symptoms between groups were SIRS (100% versus 13%, $P < 0.01$), acute diarrhea (18% versus 65%, $P = 0.01$), CRP level elevation (9.9 versus 2.1 mg/dL, $P = 0.01$), CPK level elevation (237 versus 39 U/L, $P = 0.01$), and LDH level elevation (360 versus 257 U/L, $P = 0.02$). The differences in radiological findings on CT scan were ascites collection (91% versus 17%, $P = 0.0001$) and the site of pneumatosis. Regarding the location of PI (Fig. 2), asymptomatic PI occurred more in the ascending colon as compared to pathologic PI (80% versus 47%, $P = 0.02$). Detection of PI in the jejunum and ileum was significantly higher in pathologic patients (41% versus 6%, $P = 0.01$ and 82% versus 29%, $P = 0.01$, respectively).

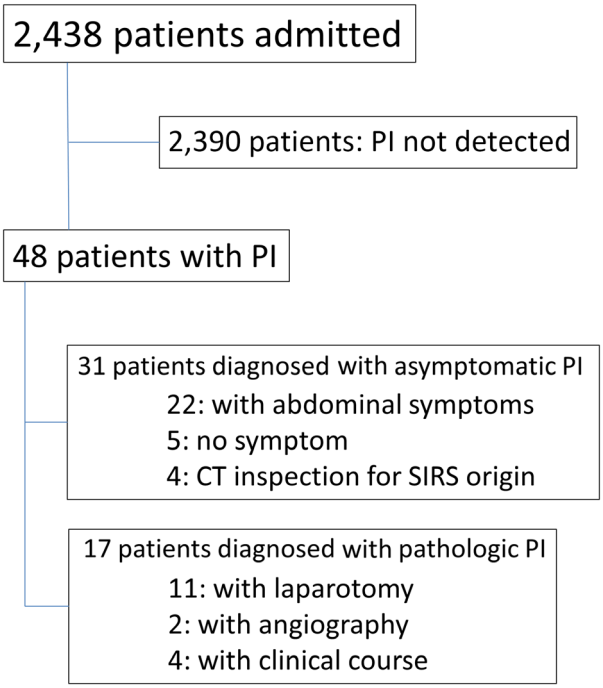

Fig. 1. Enrollment of patients, symptoms, and process of diagnosing pneumatosis intestinalis (PI). The flow diagram summarizes the selection process of the study cohort. CT, computed tomography; SIRS, systemic inflammatory reaction syndrome.

Table 1. Characteristics of patients with pneumatosis intestinalis (PI) (n = 48)

	Pathologic PI (n = 17)	Asymptomatic PI (n = 31)	P-value
Age (years)	79 (64–84)	77 (71–82)	0.97
Male sex	5 (29)	20 (64)	0.03
Diabetes	6 (35)	1 (3.2)	0.01
Initial diagnosis			
CNS disease and cervical cord injury	0 (0)	12 (39)	0.01
Trauma	7 (41)	4 (13)	0.03
Digestive disease	3 (18)	7 (23)	0.69
Sepsis	2 (12)	4 (13)	0.90
Cardiovascular disease	2 (12)	1 (3)	0.24
Clinical severity on admission			
APACHE II score	30 (21–36)	25 (17–31)	0.03
SOFA score	9 (7–13)	7 (5–11)	0.08

Data are shown as median (interquartile range) or n (%). APACHE II, Acute Physiology and Chronic Health Evaluation; CNS, central nervous system; SOFA, Sequential Organ Failure Assessment.

Table 2. Clinical status at diagnosis of pneumatosis intestinalis (PI)

	Pathologic PI	Asymptomatic PI	P-value
Hospital days, PI detected	4 (2–9)	30 (9–54)	<0.01
SIRS	17 (100)	4 (13)	<0.01
Acute diarrhea	3 (18)	20 (65)	0.01
CRP (mg/dL)	9.9 (4.7–23.8)	2.1 (0.5–4.9)	0.01
CPK (U/L)	237 (74–1172)	39 (20–71)	0.01
LDH (U/L)	360 (230–596)	257 (198–333)	0.02
Ascites collection	16 (94)	7 (23)	<0.01
Hematochezia	5 (29)	2 (3)	0.02
Portal venous gas	6 (35)	5 (16)	0.16
Operation	6 (35)	0	–
IVR	2 (12)	0	–
Hospital mortality	15 (88)	0 (0)	<0.01

Data are shown as median (interquartile range) or n (%). –, no data; CPK, creatine phosphokinase; CRP, C-reactive protein; IVR, interventional radiology; LDH, lactate dehydrogenase; SIRS, systemic inflammatory reaction syndrome.

Differentiation of asymptomatic cells from pathologic PI

Pneumatosis intestinalis centered in the ascending colon was pathognomonic in asymptomatic PI, and acute diarrhea was clinically characteristic in asymptomatic PI. The predictive values of benign and pathologic PI are listed in Table 3; showing acute diarrhea with PI in the ascending colon had a high diagnostic value for detecting asymptomatic PI. Ascites collection and PI in the ileum were characteristic of pathologic PI.

DISCUSSION

AS FAR AS we know, this is the first report differentiating the two phenotypes of PI. In this study, asymptomatic PI occurred in the post-resuscitation phase of intensive care, related to acute diarrhea, and mainly occurred in the ascending colon, without inflammatory responses.

Different gender ratios exist between the two groups in this study. In retrospective reviews of PI, the male-to-female ratio varies from equal incidence[18] to 3.5:1.[19] They included both symptomatic and asymptomatic PI. We should consider these etiologies separately, but it might be difficult because diagnosis of asymptomatic PI could have been missed.

The etiology of asymptomatic PI might be multifactorial, including mechanical overpressure of gastrointestinal gas or pulmonary gas, and bacterial overgrowth.[20]

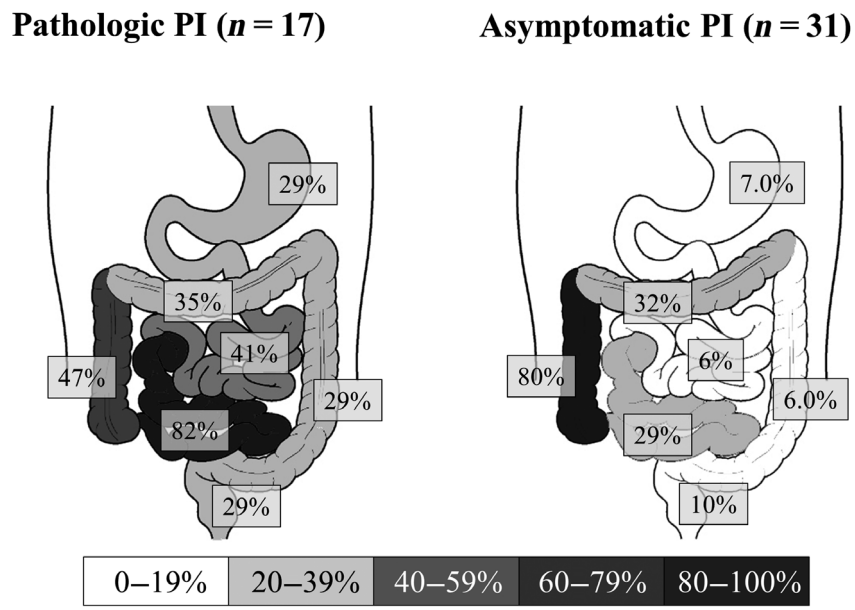

Fig. 2. Pathological characteristics of pneumatosis intestinalis (PI). Pathologic PI mainly occurred in the small intestine. Asymptomatic PI often occurred in the ascending colon.

Table 3. Diagnostic value of symptoms and signs to distinguish asymptomatic and pathologic pneumatosis intestinalis (PI)

	PPV (%)	PLR (95% CI)	Specificity (%)	Sensitivity (%)
Asymptomatic PI				
Acute diarrhea	87.0 (66.4–97.2)	3.66 (1.27–10.5)	82.4 (56.6–96.2)	64.5 (45.4–80.8)
PI in ascending colon	75.8(57.7–88.9)	1.71(1.01–2.92)	52.9(27.8–77.0)	80.6 (62.5–92.5)
Diarrhea with ascending colon PI	90.5 (69.6–98.8)	5.21(1.38–19.7)	88.2 (63.6–98.5)	61.3(42.2–78.2)
Pathologic PI				
Ascites	69.6 (47.1-86.8)	4.17 (2.15–8.09)	77.4 (58.9–90.4)	94.1 (71.3–99.9)
PI in ileum	60.9 (38.5–80.3)	2.84 (1.57–5.13)	71.0 (52.0–85.8)	82.4 (56.6–96.2)
Ascites with ileal PI	77.8 (52.4–93.6)	6.38 (2.49–16.4)	87.1 (70.2–96.4)	82.4 (56.6–96.2)
Hematochezia	83.3 (35.9–99.6)	9.12 (1.16–71.8)	96.8 (83.3–99.9)	29.4 (10.3–56.0)
Portal venous gas	70.3 (53.0–84.1)	2.19 (0.78–6.12)	83.9 (66.3–94.5)	35.3 (14.2–61.7)

CI, confidence interval; PLR, positive likelihood ratio; PPV, positive predictive value.

Diabetes treatment, especially with alpha-glucosidase inhibitor, has been reported to be associated with asymptomatic PI.[21] The drug causes abdominal distention and increases flatus due to augmented intestinal gas by bacterial fermentation of undigested carbohydrates in the bowel. This would lead to increase in intraluminal pressure and mechanically progress PI.[22] We usually used symbiotics prophylactically for all patients to avoid diarrhea. This might prevent the formation of PI by drug treatment following bacterial overgrowth. No relationship between diabetes (and alpha-glucosidase inhibitor treatment) and asymptomatic PI was observed in this study.

Diabetes is associated with risk of cardiovascular disease, including bowel ischemia. Thus, diabetes is pathognomonic in symptomatic PI.

Asymptomatic PI was characteristically observed in patients with central nervous system disease and cervical cord injury. Neurogenic bowel was observed in chronic spinal cord injury, but we could not find a relationship between central nervous system disease and cervical cord injury and acute diarrhea leading to asymptomatic PI from previous reports. In this study, many cases were in a chronic state and observed with acute diarrhea, but there was no specific information on fecal culture.

In this study, asymptomatic PI mainly occurred in the post-resuscitation phase, with acute diarrhea and poor inflammatory reaction. There was little concern with bowel/lung over-pressure due to underlying disease. In this group, gas production with bacterial overgrowth was thought to be the cause of pneumatosis. We checked fecal culture in some of the asymptomatic PI patients (14 of 21), but there were no specific findings.

Various etiologies of PI have been reported in previous studies,[23] but no relationship was reported between PI and acute diarrhea following enteral nutrition.

Concerning laboratory data, CRP, LDH, and CPK level elevation were characteristic of pathologic PI, but they reflected not only bowel ischemia, but also systemic inflammatory reactions.

There was no specific finding to distinguish between pathological and asymptomatic PI. Although portal venous gas was thought to be associated with bowel necrosis,[24] hematochezia and portal venous gas had low sensitivity in this study. We could hardly distinguish between the two groups with the degree of contrast enhancement in the affected intestine by enhanced CT.

To date, there is insufficient information regarding the location of asymptomatic PI. In this study, asymptomatic PI frequently involved the ascending colon, accompanied by acute diarrhea. It evoked bacterial overgrowth in the ileocecal mucosa. There was no evidence of *Clostridioides difficile* infection in any of the PI patients based on the results of the toxin test and fecal culture (data not shown).

Limitations of this study were its small size, retrospective nature, and the timing of CT examination; many cases of asymptomatic PI might have been missed.

CONCLUSION

IN CRITICALLY ILL patients, PI localized in the ascending colon, detected in the post-intensive care phase with poor inflammatory response, presence of acute diarrhea, and absence of ascites collection on CT, could be of diagnostic value for benign PI. Further multi-institutional studies are required to clarify patient characteristics and improve outcomes.

DISCLOSURE

Approval of the research protocol: Ethical approval was obtained from the Tohoku University Hospital Ethical Committee (2016-1-688).
Informed consent: N/A.
Registry and registration no. of the study/trial: N/A.
Conflict of interest: None.

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