Case Report

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Pathology Section

Gastric Perforation due to *Candida* Infection in Association with Prolonged Proton Pump Inhibitor Use: A Report of Two Cases

AMRITA NEELAKANTAN[1], RAKESH RAJIV PATKAR[2], SHILPA MISHRA[3]

ABSTRACT

Fungus as a cause of gastric perforation is very rare. Very low pH of stomach usually does not support fungal growth. It is usually associated with immunocompromised state or is seen in debilitated patients like patients receiving steroid therapy, patients with Diabetes Mellitus (DM) and Human Immunodeficiency Virus (HIV) infection, patients undergoing transplant. Prolonged use of strong antacids can also be a predisposing factor for gastric fungal infection; although this theory is controversial, authors could find few studies which were similar to present study. Here, authors are reporting two cases of gastric perforation leading to peritonitis, in otherwise healthy individuals due to prolonged Proton Pump Inhibitors (PPIs) use, due to *Candida* infection, in the following case report. Both patients (48-year-old male and 65-year-old female) had history of chronic PPI use, had gastric perforation and underwent exploratory laparotomy. On histopathological examination of perforation edge biopsy yeast forms and few pseudohyphae of *Candida* species were identified. Postoperatively one of the patients survived with systemic antifungal, antibiotic therapy along with replacement of PPI with histamine H2 receptor blockers. The other patient could not survive and died postoperatively due to septicaemia. Fungal aetiology in gastric perforation should prompt further evaluation to look for underlying cause. This case report highlights the effects of unjust and over use of strong antacids for prolonged period.

Keywords: Gastric candidiasis, Peritonitis, Strong antacids

CASE REPORT

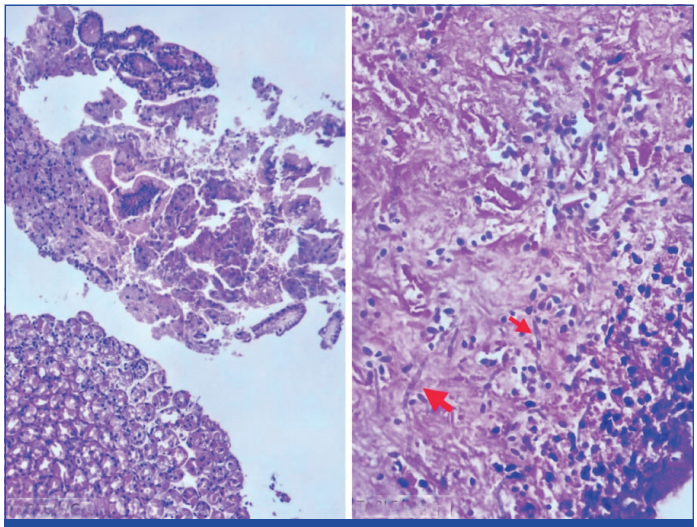
Case 1

The 1st case in this report was a 48-year-old male patient who presented in the hospital emergency room with an altered state of consciousness. He gave a history of abdominal pain for one week along with constipation and vomiting. He also complained of abdominal distension and pain for two days. There was no past history of diabetes mellitus, hypertension or tuberculosis. The patient was a known smoker with a history of occasional alcohol intake. A history of unsupervised use of pantoprazole for 4-5 months was there for abdominal discomfort. On examination, there was tenderness and guarding all over the abdomen and a liver dullness was absent. X-ray showed a moderate amount of gas under the right dome of the diaphragm. Blood profile revealed leucocytosis with neutrophilia, deranged coagulation profile, deranged liver function tests and renal function tests. On exploratory laparotomy there was bilious fluid with pus flakes all over the abdomen. There was a 1×1 cm prepyloric perforation which was repaired with an omental patch after a perforation edge biopsy was done. The gastric wall which was adjacent to the perforation was congested. The perforation edge biopsy was sent for histopathology.

Case 2

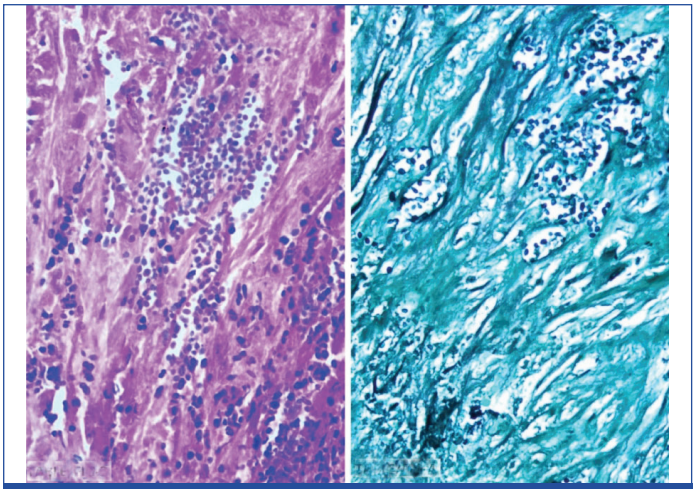
The 2nd case was a 65-year-old female patient with a history of abdominal pain, abdominal distension and vomiting for 24-36 hours. She had a past history of acid reflux for which she was taking both pantoprazole and rabeprazole for almost a year. Exact dose and schedule of drug intake was not available. On examination she had guarding and rigidity of the abdominal wall. Blood profile revealed neutrophilic leucocytosis, with hypoglycaemia and anaemia. Emergency exploratory laparotomy was performed. There was one litre of bilious fluid in the abdomen. There was a 1.2×1.1 cm perforation in the antral region which was repaired. The gastric wall which was adjacent to the perforation was indurated and swollen. The perforation edge biopsy was received in the laboratory for histopathology. The histopathological examination of both the perforation edge biopsies was performed. The tissues were processed and slides stained with Haematoxylin and Eosin (H&E) stains.

On microscopy both cases showed similar features. Perforation site showed transmural necrosis with yeast forms and pseudohyphae of fungus, morphology suggestive of *Candida* infection. Surrounding areas showed gastric mucosal epithelium with focal erosion and ulceration. Gastric glands were unremarkable. Lamina propria showed mixed inflammation composed of polymorphs, eosinophils and lymphocytes [Table/Fig-1,2].



[Table/Fig-1]: Ulcerated gastric mucosa (H&E stain; X100).
[Table/Fig-2]: Necrosis with pseudohyphae (red arrows) and yeast forms (H&E stain; X400). (Image from left to right)

Special stains of Periodic Acid Schiff's (PAS) and Gomori Methanamine Silver (GMS) were performed. They showed a positive staining in these yeast forms and pseudohyphae, which was suggestive of a *Candida* infection as a cause of the perforation [Table/Fig-3,4]. Histopathological diagnosis



[Table/Fig-3]: Yeast forms of *Candida* (H&E stain; X400); **[Table/Fig-4]:** Yeast forms of *Candida* (GMS stain; X400). (Image from left to right)

In index study, both patients were immunocompetent; however, the second patient was medically unstable after the surgery. Presence of history of chronic intake of strong antacids could have been related to fungal aetiology of gastric perforation. These finding were comparable to a case report presented by Gupta N in which an immunocompetent patient with gastric perforation presented as acute abdomen. *Candida* was diagnosed as the cause of perforation [1]. Similar case was reported by Goyal P et al., in 2016 [11]. In 2019, Kato S et al., also reported a similar case where a 59-year-old man had multiple gastric ulcers [12]. He was taking strong antacids (potassium-competitive acid blocker). His ulcer biopsy showed budding yeast forms of *Candida* after diagnosis his potassium-competitive acid blocker was replaced by H2 receptor antagonist and he recovered. Few of the studies which showed involvement of stomach by *Candida* species along with associated gastric perforation are compared in [Table/Fig-5] [1,7-9,11,12].

Author name and year	Age (years)	Gender	History of strong antacids	Other risk factors	Histopathological finding	Microbiology (culture)	Treatment	Outcome
Neelakantan A et al., Present study (2021)	48	Male	Present	Smoking	Yeast forms and pseudohyphae of *Candida*	*Candida* species	Antifungals and Antibiotics given along with histamine H2 receptor blockers	Patient recovered
	65	Female	Present	Absent	Yeast forms and pseudohyphae of *Candida*	*Candida* species	Antifungals and Antibiotics given	Patient died postoperatively
Gupta N [1] (2012)	50	Male	Present	Absent	Pseudohyphae of *Candida*.	*Candida* species	Surgical repair done	Patient died postoperatively
Bakshi GD et al., [7] (2011)	55	Male	Absent	Absent	Yeast forms of *Candida*	Not available	Antifungals given	Patient recovered
Albeiruti R et al., [8] (2020)	50	Female	Absent	Chronic obstructive pulmonary disease	Budding yeast forms of *Candida*.	Not available	Antifungals given	Patient recovered
Ukekwe FI et al., [9] (2015)	70	Male	Present	Absent	Yeast forms and pseudohyphae of *Candida*	Not available	Antifungals given	Patient recovered
Goyal P et al., [11] (2016)	45	Female	Present	Absent	Budding yeast forms of *Candida*	Not available	Antifungals given	Patient recovered
Kato S et al., [12] (2019)	59	Male	Present	Type II diabetes	Budding yeast forms of *Candida*.	Not available	Patient switched to H2 receptor antagonist	Patient recovered

[Table/Fig-5]: Few of the similar studies [1,7-9,11,12].

in both the cases was gastric perforation with invasive candidiasis. The peritoneal fluid cultures revealed colonies of *Candida albicans*. Bacterial culture was not done. The first patient was treated with combination of antifungals and antibiotics along with replacement of PPI with histamine H2 receptor blockers and survived after treatment. The second case could not survive and died postoperatively due to septicaemia.

DISCUSSION

Gastrointestinal tract can have *Candida* colonies as commensals; however, it's very unusual in stomach due low pH. Gastric perforation which is caused by *Candida* infections is uncommon and it is seen mostly in patients with immunocompromised state [1]. Patients who are on steroid therapy, in those with DM and HIV infection, in patients who are on chemotherapy are at higher risk [2,3]. The most common site involved by *Candida* infection in gastrointestinal tract is oesophagus followed by stomach, small intestine and large intestine [4-6]. Stomach involvement by *Candida* can also be seen with continuous use of antacids like PPI in immunocompetent individuals [7]. According to Albeiruti R et al., suspicion of fungal aetiology should arise when patients with peptic ulcer disease do not respond conventional treatment [8]. Few authors have suggested that pH levels affect the growth of fungi in gastrointestinal tract [9,10].

CONCLUSION(S)

Although controversial; increasing use of PPI is not without its downsides. Prolonged hypochlorhydria alters the microenvironment and may be responsible for fungal infections due to reduced mucosal defense mechanism as was seen in present cases. This is associated with significant morbidity and hence early diagnosis with a high index of clinical suspicion may save the patient from life threatening complications.

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PARTICULARS OF CONTRIBUTORS:
1. Pathologist, Department of Histopathology, Pluscare International Pvt. Ltd., Mumbai, Maharashtra, India.
2. Head and Consultant Pathologist, Department of Histopathology, Pluscare International Pvt. Ltd., Mumbai, Maharashtra, India.
3. Consultant Pathologist, Department of Histopathology, Pluscare International Pvt. Ltd., Mumbai, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shilpa Mishra,
Patkar Penthouse 25, Firuz Ara, Opposite Cooperage Garden, Nariman Point, Mumbai, Maharashtra, India.
E-mail: mishra.sm012@gmail.com

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