

Peer Review File

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Response to Reviewer A

We thank the reviewer for insightful comments, which we feel have helped us to improve our manuscript. Our specific responses to the points raised are as follows:

Comment 1: *I believe that, although no abnormal findings in the blood examinations were observed, it would enrich the manuscript to add a table with those parameters usually associated with gastroparesis (such as Na, K, BUN, etc.).*

Reply 1: We appreciate the reviewer's suggestion to improve our manuscript by adding a table containing the blood exam. The laboratory data at the onset of symptoms is shown in Table1 and are described in the Case presentation section (p. 5, lines 64–66) as follows.

Changes in the text:

Blood examinations did not show any abnormalities including acute kidney injury, liver injury, electrolyte disturbances, endocrinopathies as well as hyperglycemia (shown in Table1) .

Table1. Laboratory data at the onset of symptoms.

Variable	Reference Range†	At the onset of symptoms
Hemoglobin (g/dl)	13.7-16.8	10.6
Hematocrit (%)	40.7-50.1	32.4
Platelet count (per µl)	15.8-34.8	41.6
White-cell count (per µl)	3300-8600	9350
Differential count (%)		
Neutrophils	38-77	72.8
Lymphocytes	20.2-53.2	15.5
Monocytes	2.7-9.3	8.2
Eosinophils	0.2-4.1	3.2
Basophils	0.2-1.3	0.3
C-reactive protein (mg/dl)	0-0.14	3.5
Alanine aminotransferase (U/L)	13-30	15
Aspartate aminotransferase (U/L)	10-42	8
Alkaline phosphatase (U/L)	106-322	359
Albumin (g/dl)	4.1-5.1	2.7
Sodium (mmol/L)	139-145	138
Potassium (mmol/L)	3.6-4.8	4.5
Chloride (mmol/L)	101-108	102
Urea nitrogen (mg/dl)	8-20	9.1
Creatinine (mg/dl)	0.65-1.07	0.88
Plasma glucose (mg/dl)	60-109	104

† Reference values are affected by many variables, including the patient population and the laboratory methods. The ranges used at Kindai University Hospital are for adults who are not pregnant and do not have medical conditions that could affect results. They may therefore not be appropriate for all patients.

Response to Reviewer B

We thank the reviewer for insightful comments, which we believe have helped us to improve our manuscript. Our specific responses to the points raised are as follows:

Comment 1: *No objective gastric emptying study was performed (by scintigraphy, wireless motility capsule or breath testing) .*

Reply 1:

We appreciate the reviewer's comment on the diagnosis of gastroparesis. We agree with the reviewer that this is an important discussion point in this case presentation. Of note, however, objective gastric emptying studies including scintigraphy, wireless motility or breath testing are not approved as clinically available by the government in Japan, and we think that many other countries have the same problems. Therefore, our case presentation based on clinically practical diagnosis is still valuable for many potential readers in global population. Indeed, a previous case report of gastroparesis from Netherlands, which was published in a well-recognized hematology journal, *Bone Marrow Transplantation*, was also based on the findings from an upper gastrointestinal endoscopy and clinical histories without any data from scintigraphy, wireless motility or breath testing presented (ref 5, Jacobse J et al. Bone Marrow Transplant 2018;53:1372-4). Therefore, we believe that our case is convincing for many potential clinical readers. We already mentioned this point in the Discussion section in the original manuscript as follows (p. 8, lines 106–110):

“Gastric scintigraphy was not approved for the diagnosis of gastroparesis in our country, but we should consider that severe delayed gastric emptying could be clinically confirmed by both CT scan and EGD after complete discontinuation of enteral feeding for three days in our case, as also reported in a recent report of gastroparesis in European country (5).”

Comment 2: *Symptoms of nausea or vomiting, common in gastroparesis are not reported.*

Reply 2:

Nausea and vomiting are typical symptoms of gastroparesis, but they do not occur in 100% of patients as described in the previous article (67.9-92.9%) (Hoogerwerf W A, Pasricha P J, Kaloo A N, et al. Pain: The Overlooked Symptom in Gastroparesis

1999;94:1029-1033). In this article, abdominal pain and early satiety were also similarly common observed in gastroparesis (85.7%-89.3%), and our current case presented with upper abdominal distension that can be categorized into either of abdominal pain or early satiety, thus not excluding the diagnosis of gastroparesis in this case.

Comment 3: *It is unclear if an NGT was maintained and if that may have helped resolve the gastric distention along with the mosapride.*

Reply 3:

We already described that our case stopped the tube feeding after the onset of symptoms in the “Case presentation” section in the original manuscript as follows (p. 5, lines 67-70): “An esophagogastroduodenoscopy (EGD) after discontinuation of enteral feeding for three days showed significant impairment of gastric emptying characterized by a large amount of gastric content, although mechanical obstruction and mucosal damage were not shown (shown in Figure 1C).”

As mentioned here, we stopped enteral feeding immediately after the onset of symptoms, but the gastrointestinal distension was not improved even after three days of the discontinuation. Therefore, cessation of enteral feeding alone was not effective, given that no feeding for three days should let the gastric content being empty unless gastric emptying is delayed.

Comment 4: *Also not clear why the patient was begun on an NGT feeding at the start of chemotherapy. What prevented his oral intake at the onset of chemotherapy?*

Reply 4:

We already mentioned that the patient had a swallowing difficulty due to the oropharyngeal cancer in the “Case presentation” section as follows (p. 4, lines 50-51): “A 73-years-old male was diagnosed with human papilloma virus (HPV)–negative stage IVA oropharyngeal cancer (cT4N2bM0) as a cause of swallowing difficulty.”

It is common that patients with oropharyngeal cancer need nasogastric tube feeding during the treatment course.

Comment 5: *The patient has a subtotal gastrectomy which may have contributed to*

retained gastric contents and distention.

Reply 5:

We appreciate the reviewer's comment on the history of subtotal gastrectomy as a possible cause of his gastroparesis. We agree with the reviewer that this is an important discussion point in this case presentation. We already mentioned this point in the "Discussion" section in the original manuscript as follows (p. 7, lines 99-104): "This case experienced distal subtotal gastrectomy, but very long duration after such surgery should exclude the possibility of this prior history as a main cause of his gastroparesis. Most cases of postsurgical gastroparesis occur within one year after surgery, and the occurrence after a few years is very rare (4). The fact that this case was disease-free for more than four decades could deny the gastric surgery to be a cause of gastroparesis although this can be only very partially associated with his clinical course."

Given that no gastrointestinal symptoms have developed more than forty years after the surgery, we think that the previous subtotal gastrectomy is unlikely to be the main cause, and we should be alerted to notice that intensive neurotoxic chemotherapy can be possible cause of gastroparesis.

Comment 6: *Of note the presence of food in the stomach is not diagnostic of gastroparesis as food may be present in normal patients, depending of the MMC phase at the time of endoscopy.*

Reply 6:

Based on the previous literatures, we should think that it generally takes several hours for the stomach content to be empty after a meal in normal patient (Cassilly D, Kantor S, Knight LC, et al. Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy. *Neurogastroenterol Motil* 2008; 20: 311-319.).

As already described in our original manuscript in the current case report, an esophagogastroduodenoscopy performed after three days of discontinuation of enteral feeding showed a large amount of residual gastric contents, which should be considered an abnormal finding.

Comment 7: *It is difficult to conclude the gastric distention was chemotherapy related.*

The short duration of symptoms point away from a diagnosis of gastroparesis.

Reply 7:

As we already mentioned the cause of gastroparesis in the “Discussion” section (p. 7-8, lines 96-106), we ruled out any major causes of gastroparesis and thus suggest that intensive neurotoxic chemotherapies induced the gastroparesis.

Previous articles reporting intensive chemotherapy-related gastroparesis in hematologic malignancies also suggested a development of gastroparesis within a few weeks after the chemotherapies that is same to our current case (ref 5, Jacobse J et al. Bone Marrow Transplant 2018;53:1372-4; ref 6, Brand RE et al. The Lancet 1998;352.). Therefore, we think that the time course could not exclude the possibility of gastroparesis in our case.