POINT-BY-POINT RESPONSES

Dear Editor and Reviewers
Thank you very much for reviewing our manuscript and offering valuable advice.
We have addressed your comments and revised the manuscript accordingly.

Reviewer #1 comments
This manuscript was interesting; However, there is some concerns as fellow as:

1) *In abstract - The aim of this study should be specified in background. - the details of chemotherapy better than stated in case presentation. - Conclusion is brief, please extend it to key clinical message of this study. - Keywords was too large, please remove abundant keywords. keywords should selected according to MeSH. - Core tip was repetitive sentence that match with abstract, please revise it.*

Response: As described in the Abstract, the highlight of this study was the presentation of the utility of EUS-FNB and the possibility of paraneoplastic syndromes coexisting with GLP. We have now edited the text according to your comments, as follows:

Abstract, Page 3, line 37 to 43

> "Gastric linitis plastica (GLP) is a subset of gastric cancer with a poor prognosis. It is difficult to obtain a definitive diagnosis by endoscopic mucosal biopsies, and the usefulness of an endoscopic ultrasonography-guided fine-needle biopsy (EUS-FNB) for GLP has been recently reported. Meanwhile, autoimmune diseases are occasionally known to coexist with malignant tumors as paraneoplastic syndrome. We herein report the usefulness of an EUS-FNB for detecting GLP and the possibility of paraneoplastic syndrome coexisting with GLP."

Key words:

> Endoscopic ultrasound-guided fine needle aspiration; Linitis plastica; Autoimmune pancreatitis; Paraneoplastic syndromes; Case report

Core tip, Page 4, line 71 to 78

> "Gastric linitis plastica (GLP) is a form of gastric cancer that is difficult to diagnose by an endoscopic biopsy. An ultrasonography-guided fine-needle biopsy (EUS-FNB) is useful for diagnosing GLP with negative endoscopic biopsy findings. Meanwhile, autoimmune pancreatitis (AIP) is an IgG4-RD that occasionally coexists with gastric cancer. Some cases of IgG4-RD have been reported to be improved by the treatment of malignant tumors, suggesting that IgG4-RD may develop as a paraneoplastic syndrome. From the clinical course and image findings, we experienced a suspected case of AIP developed as paraneoplastic syndrome coexisting with GLP."

2) *Introduction - the sentence "Gastric linitis plastica (GLP) is a subset of gastric cancer with a poor prognosis, showing a frequency of 8%-17% among overall gastric cancers" need for citation. Introduction - Introduction was small, please discuss about diagnostic criteria, patient management guidelines as well as molecular mechanism behind the tumor.*

Response: In the Introduction, we added reference No. 1 to the sentence, "Gastric linitis plastica (GLP) is a subset of gastric cancer with a poor prognosis, showing a frequency of 8%-17% among overall gastric cancers." In addition, we mentioned the diagnostic criteria for and molecular mechanisms involving IgG4-RD. We also added the following text:

Introduction, Page 4, line 90 to 107

"Immunoglobulin G4 (IgG4)-related disease (RD) is characterized by the infiltration of lymphocytes/plasma cells with fibrosis in the lacrimal/salivary glands, pancreas, lungs, bile ducts, kidneys, retroperitoneum, and other organs, causing various symptoms. High numbers of IgG4-positive plasma cells are seen in the affected organs, and elevated serum IgG4 levels are also observed[3]. The diagnostic criteria of the Japanese IgG4-RD guideline include three domains: clinical and radiological features (i.e. ≥1 organs show diffuse or localized swelling), a serological diagnosis (i.e. serum IgG4 levels >135 mg/dl), and a pathological diagnosis (e.g. IgG4/IgG-positive cells >40%)[4]. "

However, IgG4-RD is also known to be associated with malignant tumors, and some have reported that chronic inflammatory stimulation was involved, although the exact mechanism has not been elucidated[5]. One pathway, involving interleukin-33, which plays a role in the pathogenesis of IgG4-RD, has also been reported to be associated with the development of malignancy[6, 7]. In particular, autoimmune pancreatitis (AIP) is an IgG4-RD that occasionally coexists with gastric cancer. Some cases of IgG4-RD, including AIP, have been reported to be improved by the treatment of malignant tumors, suggesting that IgG4-RD may develop as a paraneoplastic syndrome[8]."

3) *Case presentation - the author should give more details regarding imaging examination, histopathological results, as well as treatment regimen (dosage and duration).*

Response: Regarding imaging examinations, we added the following:

Case presentation, Page 7, line 154 to 156

"No other organ involvement complicating AIP and no obvious metastasis of GLP nor swollen nodules in which FDG had accumulated were observed."

Regarding histopathological examinations, we added the following:

Case presentation, Page 7, line 177 to 179

"No cancer cells were found in the shallow site of the mucosa. In the muscularis mucosae, fibroblasts had proliferated and were considered to be the cause of gastric wall thickening."

Regarding treatment, we clearly described the regimen dosage and duration. We also mentioned the treatment for AIP.

Case presentation, Page 8, line 195 to 200

"The patient then received first-line chemotherapy with a postoperative FOLFOX plus nivolumab regimen (5-fluorouracil, leucovorin, and oxaliplatin: 5-fluorouracil 400 mg/m2, day 1 and 1200 mg/m2, days 1–2, leucovorin 400 mg/m2, day 1, oxaliplatin 85 mg/m2, day 1; and nivolumab 240 mg, day 1, every 2 weeks). There were no symptoms of AIP, such as abdominal pain or jaundice, and there was no evidence of involvement of other organs. Therefore, treatment for AIP was deemed unnecessary."

4) *Discussion - Please discuss about previous relevant cases. - the author should also discuss about limitation of this study.*

Response: Previous cases of EUS-FNB for GLP are summarized in Table 2. The complications of GLP and AIP are summarized in paragraph 5. Reports indicated that gastric cancer is found in 1.3% of AIP patients. Regarding the link between autoimmune diseases and malignancy, there is a theory that chronic inflammation caused by autoimmune diseases triggers carcinogenesis, and there have been reports that interleukin-33 is involved in this process. Another theory is the concept of paraneoplastic syndrome, in which malignant tumors trigger autoimmune diseases. The report by Shiokawa et al. discussed the possibility of AIP developing as a paraneoplastic syndrome, with the reported rationale being that some AIP patients had a high risk of malignancy within one year of the diagnosis of autoimmune disease, and the clinical course differed between cases with and without malignancy, with treatment for malignancy reducing the relapse rate, which was consistent with the features of paraneoplastic syndrome.

Regarding the limitations associated with this report, we referred to the inability to perform a biopsy of the pancreatic tissue and differences between our case and the cases reported by Shiokawa et al. We have now added the below text to paragraph 5.

Discussion, Page 10, line 258 to 290

"The correlation between GLP as cancer and AIP as an autoimmune disease remains unclear; however, IgG4-RD is known to be associated with malignant tumors. One possibility is carcinogenesis due to chronic inflammation. In patients with IgG4-RD, it has been suggested that stimulation from chronic inflammation may trigger carcinogenesis, and one such pathway involves interleukin-33, which plays a role in the pathogenesis of IgG4-RD and is also associated with malignancy[5-7]. Tumor secretion of hormones, peptides, and cytokines or immune cross-reactivity promote the onset of

autoimmune disease, widely known as paraneoplastic syndrome[25], which is separate from the carcinogenic pathway due to chronic inflammation. Shiokawa et al. reported that 15 of 108 AIP patients had malignancy, with a standardized incidence rate (95% confidence interval [CI]) of cancer within 1 year of the AIP diagnosis of 6.1 (95% CI 2.3-9.9) and 1.5 (95% CI 0.3-2.8) beyond 1 year after the AIP diagnosis, indicating a higher risk of cancer within 1 year of the AIP diagnosis than beyond it. In addition, serum IgG4 levels were significantly higher in AIP patients with cancer than in those without cancer. Furthermore, only 1 of the 8 AIP patients with cancer, whose cancer was resected prior to steroid therapy for AIP had a relapse of AIP, whereas 16 of the 93 AIP patients without cancer had a relapse[26]. In short, some patients with AIP had a high risk of malignancy within one year of the diagnosis of autoimmune disease, and the clinical course differed between cases with and without malignancy, with treatment for malignancy reducing the relapse rate, which was consistent with the features of paraneoplastic syndrome. Therefore, some AIP may be caused by the same mechanism. In the present case, AIP was diagnosed at the same time as GLP, and the serum IgG4 level was as high as 280 mg/dl. After the start of chemotherapy for GLP, both the CT findings of the pancreas and the serum IgG4 level improved along with GLP, and the patient was free from relapse of AIP. These results suggested that the AIP in the present case developed as paraneoplastic syndrome."

And in paragraph 6.

"Nevertheless, a pancreatic tissue biopsy by an EUS-FNB is preferred for the diagnosis of AIP. A pancreatic tissue biopsy should be considered in similar cases in the future. In addition, Shiokawa et al. reported a reduced AIP relapse rate after resection of malignancy as a feature of AIP as paraneoplastic syndrome. However, the present case differed in that the tumor was not cured by resection but rather shrunken by chemotherapy[26]. The accumulation of similar cases and further studies on autoimmune disease as paraneoplastic syndrome are also needed."

5) *Conclusion - Conclusion should be objective contain clinical key message as well as further perspective to future research.*

Response: Autoimmune disease associated with malignancy may be paraneoplastic syndrome and may improve with treatment of the malignancy. Therefore, its diagnosis and treatment should be done carefully. We have now added the following:

Conclusion, Page 12, line 295 to 297

"Furthermore, autoimmune disease that develops as a paraneoplastic syndrome should be carefully diagnosed and treated, as they may be able to be improved with a reduced likelihood of relapsing following treatment of the original malignant disease."

Reviewer #2 comments

I read with interest the case report about Gastric linitis plastics and IgG4 RD. Although an interesting case I find difficult to prove a casual effect of gastric cancer as promotor of autoimmune pancreatitis. As the authors correctly stated, relationship between neoplasia and autoimmune pancreatitis has been difficult and controversial. It would have been helpful to have prior imaging records of the patient showing the pancreas and if those changes did or did not exits prior to the gastric ones. Considering a "possible" response to chemotherapy as a diagnostic criteria is difficult to accept since the effects of FOLFOX on the WBC count may be accountable for the decrease in IgG4 and improved pancreas imaging and not necessarily proves that AIP was a paraneopalstic manifestation. It could well coexist. Providing EUS imaging after QT would be informative as well as a figure comparing CT imaging of pancreas before and after treatment.

Response: Unfortunately, we do not have radiographic images of the pancreas prior to admission to our hospital or EUS images of the pancreas after the start of chemotherapy. As you note, if we had access to these, we could emphasize the correlation between GLP and AIP as paraneoplastic syndrome. CT findings of the pancreas after chemotherapy are shown in Figure 5C. Chemotherapy improved the CT findings of diffuse enlargement of the pancreas. The accumulation of similar cases and further studies on autoimmune disease as paraneoplastic syndrome is needed. We also revised our manuscript to mention the possibility of paraneoplastic syndrome, as advised by other reviewers. I believe that these corrections will prove suitable for responding to your comment.

Reviewer #3 comments

Dear Authors, Thank you for conducting this study entitled "Gastric linitis plastica with autoimmune pancreatitis diagnosed by an endoscopic ultrasonography-guided fine-needle biopsy: A case report" for possible publication in the esteemed journal "World Journal of Gastroenterology". The article needs to be revised according to my comments in the main manuscript file. Best regards

1) *It (in case summary) needs some detail regarding the history of the present illness.*

Response: We have now added a case summary.

Abstract, Page 3, line 46 to 47

"An 81-year-old man was admitted to our hospital for a 1-month history of epigastric pain that increased after eating."

2) *It (Present illness) needs more detail.*

Response: We have now added the history of the present illness.

Case presentation, Page 5, line 118 to 120

"His pain increased after eating. He had undergone esophagogastroduodenoscopy (EGD) at the previous hospital, which showed findings suggesting GLP. He was therefore admitted to our hospital for further examinations."

3) *It (Physical examination) needs some detail.*

Response: We have now mentioned the abdominal examination findings and Virchow's lymph nodes, with the following added:

Case presentation, Page 6, line 131 to 132

"His vital signs were normal, and the abdomen examination revealed mild epigastric tenderness and no guarding or rebound tenderness. He had no swollen Virchow's lymph nodes or parotid or lacrimal glands."

4) *They (Table 1) need the reference range of each one.*

Response: We have now added the reference range to Table 1.

5) *It (Table 2) is better to mention the country of the study.*

Response: We have now mentioned the country in Table 2.

Thank you for offering valuable advice. I look forward to hearing from you.

Sincerely,

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