

Peer Review File

Article Information: <http://dx.doi.org/10.21037/apm-21-940>

Reviewer A

Case is interesting as a malignancy arising from outside of the esophagus causing stricture and dysphasia is uncommon. However, the focus of this case report is on the use of a nasogastric tube to treat significant dysphagia with malnutrition and problems of administering medications is not novel at all. The fact that the disease responded well to osimertinib and the dysphagia improved is not unexpected if the drug has proven efficacy.

Abstract: Line 27-28: Missing out on oral osimertinib did not cause severe malnutrition. It is from the lack of nutrients from poor oral intake. Suggest "The esophageal stricture hampered food intake and oral administration of osimertinib, causing severe malnutrition and deterioration to performance status 3."

Response:

I am sorry for the wrong description and I rephrased as you suggested.

Line 65: How can you tell if the stenosis is caused by external and not intramural pathology from EGD? You can only state that it is not caused by a mucosal abnormality from EGD. No mention of what calibre gastroscop was used and whether the scope could go pass the stricture into the lower esophagus. This detail is important to allow readers to appreciate how tight the stricture was.

Response:

I really appreciate your important suggestion and I agree with your opinion.

I have changed the relevant sentence to accurately describe the findings of EGD, and added the caliber of EGD.

The relevant sentence was changed into "Esophagogastroduodenoscopy (EGD) with a distal end diameter of 5.4mm revealed severe and entire circumferential stenosis (7 cm in length, through which the EGD could pass) of the upper esophagus without mucosal abnormality (Figure C)".

How severe was the malnutrition and how was the "severe malnutrition" addressed? The patient seemed to have a rather high body mass index based on the thickness of subcutaneous fat on the CT scan images. There was no mention of using the nasogastric tube for feeding other than administering medication. If the nasogastric tube was not used for feeding, was parenteral nutrition provided instead?

Response:

I really appreciate your important suggestion. The peripheral parenteral nutrition was not effective in the current case. Nasogastric tube feeding was not selected since the patient was cachexic.

I changed the sentence into "The esophageal stricture also caused severe malnutrition, which did not respond to the peripheral parenteral nutrition, and deterioration to performance status (PS) 3".

In fact, weight loss by 3kg was observed during the first 2 weeks after admission. I avoided writing this observation in order to avoid redundancy.

Lines 79-80: "Esophageal strictures are divided into simple and complex, according to the shape of the surfaces and margins, or the width and length of the opening." Suggest deleting this sentence as it is not the clear and not the conventional way of classifying esophageal stricture that can guide treatment. Suggest to focus your discussion on management of malignant strictures.

Response:

I really appreciate your sincere advice and suggestion. I agree with you in that the relevant sentence is redundant, and I deleted it.

Lines 80-81: Suggest rephrasing to: Cancerous strictures tend to cause more rapid symptoms progression than benign strictures.

Line 86: However, swallowing medication "in tablet form" is difficult in patients with esophageal stricture.

Response:

I really appreciate your sincere suggestion and I have rephrased two sentences along your advice.

Reviewer B

Your case report is an interesting approach to an unusual problem. A few questions; 1. Were you concerned about the esophageal mucosa, was there any invasion of the esophagus by the LN or only external compression? 2. Did you consider longer term enteral access such as a PEG given the dysphagia? Patient often do not like NGTs or Dobhoffs for long periods. 3. Were there any adverse outcomes from an NGT in place for so long?

Response:

I really appreciate your sincere suggestion and advice. I agree with your opinion and added some explanations.

No.1: The mucosal abnormality was not observed via EGD. Then, I changed the relevant sentence into “Esophagogastroduodenoscopy (EGD) with a distal end diameter of 5.4mm revealed severe and entire circumferential stenosis (7 cm in length, through which the EGD could pass) of the upper esophagus without mucosal abnormality (Figure C)”.

No.2: PEG was not performed since the patient did not want it. Then, I added a sentence “Percutaneous endoscopic gastrostomy was not performed since the patient refused the procedure”.

No.3: There were no adverse outcomes from an NGT placement for 3 weeks. I did not add this information this time, since the Case Report section could be redundant.

Reviewer C

Nozomi Tani et al present a case report describing mediastinal lymphadenopathy for an EGFR mutation harboring adenocarcinoma causing dysphagia. They describe the use of an osimertinib suspension as a method of administering the agent in patients who are unable to swallow pills. The patient described in this report has a good response with resolution of dysphagia within 15 days.

At this time, it is unclear what is novel about this report that warrants publication. The use of EGFR TKI suspensions via nasogastric tube has been previously described in patients with dysphagia. This has been cited by the authors as well. Though the use of

osimertinib may not have been described, the authors in the discussion do explain that the chemical formula and coating agents are similar. As such, the use of osimertinib via NG does not warrant a case report.

Response:

I really appreciate your important suggestion and critique.

As you pointed out, EGFR-TKI administration via nasogastric tube has been previously reported. However, the cause of dysphagia in the previous reports is intracranial lesions, such as leptomeningeal metastases (Reference No. 2, 4) or bulky metastasis beside the medulla (Reference No. 3). I cannot find out a case of EGFR-TKI suspension administration due to esophageal stricture. Therefore, I believe that the current case is unique in its pathophysiology.

The presence of esophageal obstruction secondary to mediastinal lymphadenopathy is also not a rare phenomenon. This has been encountered with many cancers; with lung cancer being the most common culprit. In this disease process the use of palliative mediastinal radiation and esophageal stenting has also been well described to improve dysphagia symptoms. A discussion regarding why an NG tube was used here compared to those other options in patients with EGFR sensitizing mutations may make this case report more informative. For example the use of an esophageal stent may cause inadvertent airway compression in the presence of lymphadenopathy.

Response:

I really appreciate your suggestion. I agree with you in that esophageal stricture caused by lung cancer is not rare. However, most of these cases are usually treated by palliative radiotherapy or esophageal stenting. Radiotherapy needs a couple of months for its effect and usually worsens the esophageal stricture by transient mucosal edema by irradiation. Therefore, I believe that the administration of molecular targeting agent for the appropriate case would be the best way to reduce the tumor burden and relieve the relentless symptom of dysphasia.

The reason why we did not use an esophageal stent in the current case was the risk of stent dislocation after expected tumor shrinkage by osimertinib. This could be helpful for readers, and I added one sentence in the Case Report section; “Self-expandable metallic esophageal stent deployment could be one option, which was not adopted in the current case considering the risk of stent dislocation after shrinkage of lymph node metastases by osimertinib”.

In line 59, it is unclear what is meant by semi-flexible thoracoscopy. Does this mean endoscopy through the esophagus as is shown in figure c? Additionally, endoscopy cannot demonstrate a pathological finding of adenocarcinoma with a mutation. I would reword this to state the biopsy from the esophagoscopy revealed adenocarcinoma harboring EGFR mutation.

Response:

I am sorry for difficult description. The semi-flexible thoracoscopy is one of the thoracoscopy which is usually used under topical anesthesia. Thoracoscope is a standard way to examine pleural disease including pleural dissemination. The current case is cT2aN3M1a, stage IVA, which mean the carcinomatous pleuritis. Thus, the biopsy was obtained from pleural dissemination via the semi-flexible thoracoscopy in the current case, and the accurate diagnosis was made.

Overall, though this is an interesting case the report does not reveal sufficient novel or rare findings that warrant publication as a case report.

Response:

I believe that the above-mentioned responses would help you understand the novelty of the current case.

I really thank you for letting me know some parts of our description which are difficult to understand.

Reviewer D

Good case and well written. I suggest changing the title to "Nasogastric Administration of Osimertinib for an EGFR-mutated lung cancer causing an Esophageal stricture" or something along this line to highlight the main point of this case.

Response:

I really appreciate your sincere suggestion and I agree with your opinion.

I have changed the title to "Nasogastric administration of osimertinib suspension for an EGFR-mutated lung cancer causing an esophageal stricture: case report".