AOE ANNALS OF ESOPHAGUS
A JOURNAL FOCUSING ON BASIC AND CLINICAL RESEARCH IN THE FIELD OF ESOPHAGUS

Peer Review File

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Review Comments

This manuscript shared a case report which a non-HIV 71-year-old male showed recurrent esophageal candidiasis with five complicated complications. The authors aimed to raise the consciousness of esophageal candidiasis for non-immunosuppressed patients. This manuscript is potentially publishable at Annals of Esophagus. However, quite a lot of issues listed below need the authors' concern.

Major concerns
1. This manuscript was written in the way of non-evidence-based. For example, there are no references to support "Esophageal candidiasis is an infection with multiple known rare complications and is commonly encountered in immunosuppressed patients." (line23), "However, it is rarely encountered in patients with intact host defense mechanisms."(line25), "there may be gaps"(line 26. what gaps? are you not sure? why you use "may be" instead of a definite finding?), "can result in inadequate treatment and increased complications."(line28).

Make sure all points are well supported with high-quality evidence. Similar mistakes are also shown in the discussion part.

Reply 1:

- References have been added to support statements within the introduction
- Gaps – the point has been clarified that due to low rates of esophageal candidiasis occurring in non-HIV patients, there is lesser screening/suspicion for asymptomatic candidiasis which can be easily eradicated. The complications of esophageal candidiasis have too been clarified.

Changes in the text: Page 2, lines 38-46

- Esophageal candidiasis is an infection with multiple known rare complications and is commonly encountered in immunosuppressed patients. (1)
- However, symptomatic esophageal candidiasis is rarely encountered in patients with intact host defence mechanisms, despite the fact that Candida can colonize the esophagus in up to 20% of healthy adults. (2, 3)

- Due to the rare occurrence of symptomatic esophageal candidiasis in non-HIV patients, surveillance such as screening endoscopy is too costly and invasive to be used in this population group. (4, 5) As a result, asymptomatic esophageal candidiasis, which is easily treatable, can go unnoticed, resulting in inadequate treatment and increased complications such as esophageal perforations, fistula formations and development of mitotic lesions. (6,7)

2. The phrasing is not rigorous or precise, which leads a considerable misleading. For example, "there have been no prior reports of esophageal candidiasis complicated by dysphagia, food bolus obstruction, benign stricture, ulceration and hyperkeratosis, all present in one patient."(line115~118). This point is not correct! There are so many cases that have reported these complications. It's just these complications did not show at the same time on one patient!
Check through the manuscript and make sure all points are precise.

Reply 2:

- The phrasing has been changed to more clearly reflect that our patient suffered from all the complications rather than singular complications

Changes in the text 2: Page 6, Lines 142-145

- Despite the many known complications of esophageal candidiasis, there have been no prior reports of a single patient presenting with esophageal candidiasis complicated by all the following: dysphagia; food bolus obstruction; benign stricture; ulceration, intramural pseudodiverticulosis and hyperkeratosis.

3. The so-called 10-year is misleading and not accurate. As we know, the diagnosis of esophageal candidiasis was not diagnosed until 2017. Before 2017, have authors done the fungal test? If not, how could authors be sure of this? In fact, it might be correct. However, all are based on suspicions.

In this occasion, two years would be a more rigorous point. Authors could discuss the long-term in the discussion part.

Reply 3:

- The title has been updated to remove “decade”
- The lack of fungal testing has been included as a limitation, with emphasis on the lack of clarity of the impact of a possible long-standing colonization/esophageal candidiasis on the complications experienced by our patient

Changes in the text:

- Title: **(Page 1, line 2):** Recurrent esophageal candidiasis: a case report of

different complications

- Conclusion: **(Page 9, lines 212-217):** Secondly, our patient was only formally diagnosed with esophageal candidiasis in 2017 based on fungal testing, and it is unclear if our patient was colonized with candida or was symptomatic with esophageal candidiasis since the start of his symptoms in 2007. This makes it unclear as to the effect of possible long-standing esophageal candidiasis on his esophageal stricture and hyperkeratosis, and if earlier treatment could have prevented these complications.

4. Regarding this non-immunosuppressed patient, the present point is not rigorous.

For example, the patient is now 71 years old. The patient immune status would probably not that good, not even mention his complex history (diabetes, heart disease, hypertension, smoking, drinking, etc.). So, authors need to discuss this.

Besides, it's not until 2019.8 that authors did the HIV test, though it's negative. As we know, HIV has quite a long history of latent phage (over ten years). How we see, he's not an HIV-patient? This should also have been well discussed in the discussion.

Reply 4:

- We agree that the patient's age and complex medical history contribute a degree of immunosuppression, even in the absence of HIV.

Changes to the text: Page 9, lines 207-212

- Firstly, we assumed the immune status of our patient to be non-immunosuppressed based on his negative HIV serological testing and clinical presentation. However, his age and past medical history of diabetes mellitus may have contributed a degree of immunosuppression as well. Furthermore, HIV testing was only conducted in 2019, and although it was negative, HIV testing is well associated with false negatives in its latency phase, and ideally serial HIV testing should have been conducted given his recurrent candidiasis. (20)

5. Regarding the fungal status. It's not clear whether the test has been done every time during 2007, 2009, 2013, 2017, 2018.9, 2019.8 and 2019.11. I only found one place that clearly explained this test was done.

Reply 5:

- No flexible endoscopy or biopsy was performed in 2007 and 2009. Only rigid esophagoscopy and disimpacting of food bolus was performed. Fungal testing

was performed in 2013 (negative on biopsy stain), 2017 (positive on biopsy), 2018 (positive based on scope findings although fungal testing was negative), 2019 (positive on biopsy and fungal cultures).

Changes in the text:

- Fungal testing proved negative **(Page 4, line 74)**
- Biopsy from the esophagus showed acute erosive esophagitis and returned positive for fungal organisms **(Page 4, lines 81-82)**

6. The most significant point is that what's the clinical value of this case report? On the one hand, it could help peers better diagnose among non-HIV patient. But, the authors should have made this more step-by-step clear. On the other hand, useful therapies would also shed light on future treatment for peers. However, this case was diagnosed since 2017 while has relapsed twice, proving that the procedure is not that great. What's our next step to better treat such patients from this case report?
Other concerns

Reply 6:

- Clinical value of this case report is 2-fold
    - To develop a higher clinical suspicion for esophageal candidiasis even in immunocompetent patients and have earlier fungal testing and anti-fungal therapy
    - To highlight the complications of long standing esophageal candidiasis and hyperkeratosis, namely mitotic lesions, which can possibly be averted with earlier detection and eradication of the candidiasis.

Changes to text:

- Introduction: **(Page 2, lines 50-51)** We aim to highlight the importance of developing a higher level of clinical suspicion for esophageal candidiasis and recognizing possible complications that may arise.
- Discussion: **(Page 9, lines 219-224)** In conclusion, clinicians should have a lower threshold for considering esophageal candidiasis even in non-immunosuppressed patients presenting with esophageal symptoms and have earlier consideration of esophageal biopsies and fungal testing and ensuing fungal eradication therapy if indicated. Our case report also serves to educate readers on the possible clinical presentation, disease progression and complications that may arise from chronic esophagitis and recurrent esophageal candidiasis.

7. Title: the title needs refining according to the comments above.

Reply 7:

- Title has been updated accordingly.

Changes to text: (Page 1, line 2)

- Title: Recurrent esophageal candidiasis: a case report of different complications

8. Abstract: 200~350 words are required. Also, background information is suggested. Besides, highlight what is unique of this case in the abstract. Make sure the take-away lesson is right, accurate, and practical. And, the dosage has changed, please mention that too (200mg→400mg-200mg).

Reply 8:

- The abstract word count has been increased to 245. The abstract has been updated to reflect the following:
    - Uniqueness of the case: first case report of esophageal candidiasis complicated by strictures and hyperkeratosis
    - Major complications of strictures (esophageal perforation and fistula formation) and hyperkeratosis (mitotic lesions)
    - Takeaway lesson: to develop a higher suspicion for esophageal candidiasis in non-immunosuppressed patients
- The dosages of fluconazole in each of the 3 years was 3/52 of 200mg OM after a loading dose of 400mg. There was no change in the patient's dosage in each episode.

Changes in the text 8: (Page 1, lines 19-35)

A 71 year-old male patient presented with recurrent acute dysphagia in 2017 on a background of previous episodes of upper esophageal food bolus obstruction and mild gastro-esophageal reflux disease several years ago. He was diagnosed with acute erosive esophagitis from candidiasis and chronic gastritis with intestinal metaplasia. These were treated with anti-fungal therapy and a proton pump inhibitor. A year later, he had recurrent dysphagia and found to have upper esophageal stricture and diffuse esophagitis with ulceration and hyperkeratosis. The same treatments were given but his problems recurred again another year later. Recurrent candidiasis was confirmed on esophageal biopsy and fungal culture. He was treated with a third course of anti-fungal therapy with good resolution of dysphagia symptom, esophagitis and stricture, both clinically and endoscopically. Intramural pseudodiverticulosis of the upper esophagus was also evident during endoscopy and barium swallow study. Hyperkeratosis was persistent. He is planned for surveillance endoscopy for persistent esophageal hyperkeratosis and chronic gastritis with intestinal metaplasia. Ulceration, stricture, intramural pseudodiverticulosis and hyperkeratosis are the less common complications of esophageal candidiasis that we have seen all occurring on this patient. These may be further complicated by perforation or fistula formation from the inflammation and strictures, and mitotic lesion from hyperkeratosis. In conclusion, we should develop a higher level of clinical suspicion for esophageal candidiasis and recognize possible

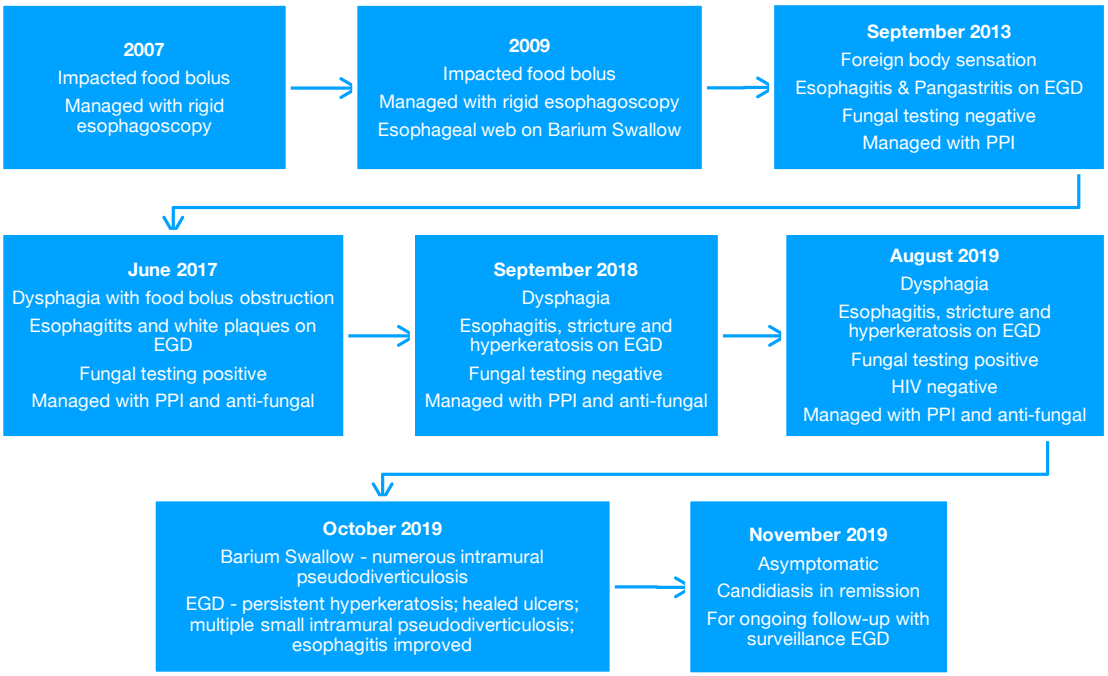
complications that may arise in severe, chronic or recurrent disease, in patients with recurrent esophageal symptoms, in order to treat them effectively.

9. Case presentation.
9.1 Draw a timeline to outline the whole process. Make sure it stands alone.
9.2 Add information regarding the CARE guideline checklist item 9b, 9c, and 10c.

Reply 9:

- A concise timeline has been included
- CARE guidelines checklist
  - 9b – included previously, no change
  - 9c – not relevant
  - 10c – included previously, no change

Changes to text: Page 3, line 58



10. Discussion
10.1 Among the five focused complications, only three were discussed. The discussion of the rest two—dysphagia and ulceration were missing.
10.2 There're no take-away lessons in the end.
10.3 Add one separate paragraph to list both strength and limitations of this case report.

Reply 10:

- Dysphagia associated with stricture formation, and intramural pseudodiverticulosis (which is a more accurate description of the "ulcers" seen on barium swallow and the latest endoscopy) are also discussed.

- Limitations have been included as the penultimate paragraph.
- Conclusion and take-away points have been included in the final paragraph.

Changes to text:

- **(Page 6, lines 147-152)** Dysphagia is one of the commonest symptom of esophagitis which, in chronic disease, can be a manifestation of stricture formation and it may progress to cause food bolus obstruction. The most common cause of esophageal stricture is gastresophageal reflux. For our patient, he did have mild gastro-esophageal reflux disease as evident from the earlier barium study and esophageal biopsies showed moderate reflux esophagitis. Whether the reflux disease contributed to candidiasis and the upper esophageal stricture remains unknown.
- **(Page 7, lines 167-176)** Intramural pseudodiverticulosis is an interesting finding that is less commonly reported. (10-12) The wall of the esophagus develops numerous small outpouchings. The outpouchings represent the ducts of submucosal glands of the esophagus. Pseudodiverticulae may also be seen on barium swallow imaging of the esophagus as flask-shaped pseudodiverticulae. While it is associated with certain chronic conditions, particularly alcoholism, diabetes and gastroesophageal reflux disease, the association with esophageal candidiasis is less well established, with very few case reports published (10, 12). It has been hypothesised that pseudodiverticulae are not a primary phenomenon, but rather are secondary to a chronic irritant to the esophagus, leading to compression of the submucosal ducts and the formation of pseudodivericulae. (10) The most relevant complication is the development of esophageal stricture which is mainly localized in the upper esophagus. (11, 12)
- **(Page 9, lines 207-217)** There are some limitations of our case report. Firstly, we assumed the immune status of our patient to be non-immunosuppressed based on his negative HIV serological testing and clinical presentation. However, his age and past medical history of diabetes mellitus may have contributed a degree of immunosuppression as well. Furthermore, HIV testing was only conducted in 2019, and although it was negative, HIV testing is well associated with false negatives in its latency phase, and ideally serial HIV testing should have been conducted given his recurrent candidiasis. (20) Secondly, our patient was only formally diagnosed with esophageal candidiasis in 2017 based on fungal testing, and it is unclear if our patient was colonized with candida or was symptomatic with esophageal candidiasis since the start of his symptoms in 2007. This makes it unclear as to the effect of possible long-standing esophageal candidiasis on his esophageal stricture and hyperkeratosis, and if earlier treatment could have prevented these complications.
- **(Page 9, lines 219-224)** In conclusion, clinicians should have a lower threshold for considering esophageal candidiasis even in non-immunosuppressed patients presenting with esophageal symptoms and have earlier consideration of esophageal biopsies and fungal testing and ensuing fungal eradication therapy if indicated. Our case report also serves to highlight the possible clinical

presentation, disease progression and complications that may arise from chronic esophagitis and recurrent esophageal candidiasis.