Author’s response to reviews

Title: Two cases of granuloma mimicking local recurrence after pulmonary segmentectomy

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Version: 1 Date: 23 Dec 2019

Author’s response to reviews:

We wish to express our appreciation to the reviewers for their insightful comments on our paper. The comments have helped us significantly improve the paper.

Reviewer #1: Thank you for your valuable papers for the journal.

1. What is the postoperative pathological stage of case 1? AAH,AIS,MIA or IA, We know that had a very good survival rate at the previous MIA stage. Did you consider these factors when you found a recurrence of pulmonary nodules?

Response: We appreciate the reviewer's comment on this point. The pathological diagnosis of case 1 was minimally invasive adenocarcinoma stage IA. We know that MIA patients have good prognosis considered these factors as you mentioned, but we sometimes experience the local recurrence of MIA as well when the patient underwent limited surgery such as segmentectomy and partial resection. In the present cases, CEA elevation and FDG uptake made us strongly suspect the local recurrence. On the other hands, we wanted to avoid losing the chance of operation due to tumor progress and dissemination, because course observation may be at risk for them.

2. Please add the chest CT image after recurrence. In case 2, I can see lung nodules with long burrs, which generally indicates the possibility of benign nodules. If other malignancies are considered lung metastases, they are generally manifested as multiple round nodules along the vascular branch.

Response: We added the chest CT image. As you mention, we often experience lung benign nodules with long burrs, but in the case 2 these long burrs are suture line made by previous operation. Although there had been long thin burrs postoperatively, nodules have grown in the part of these burrs.
3. These nodules after lung surgery and this is like a piece of clothing, you get wrinkles when you sew it up.

Response: We paste PGA sheets by using fibrin glue on the segmental plane without sewing.

4. Pulmonary hemorrhage is a major challenge for thoracic surgeons, and we can consider blocking the pulmonary artery. The right pulmonary artery is deep and can be found below the fourth group of lymph nodes, in front of the trachea and behind the superior vena cava.

Response: We should have blocked the right main pulmonary artery before we touched the pulmonary artery to reduce bleeding as you mention. Although we knew that reoperation is usually difficult and involves substantial risk as well, we thought we could finish the operation without clamping pulmonary artery when we observed pulmonary artery at the beginning of the operation.

Reviewer #2: Dear Professor Zamvar and authors,

It was my pleasure to review this case report manuscript submitted by Dr. Okazaki and his colleagues from the Center of Chest Medicine and Surgery at Ehime University of Japan in which they present two patients which developed granulomas at the sites of their previous resections for malignancy and which due to false positive findings in the PET CT scans and in CEA underwent quite laborious and challenging repeat resections. I apologize to you and the authors for the small delay in returning my review.

The manuscript is well presented and structured, with relatively good English but it does require some minor expression, tense and language correction by a native speaker or a professional editing service. The patient presentations are good and the images supplied are adequate, although maybe the extensive histology is not needed.

Response: The paper has been edited and rewritten by an experienced scientific editor, who has improved the grammar and stylistic expression of the paper. We attach the certificate of English editing. However, we will use other editing service if there are still English problems.

That having been said, this reviewer fails to see the educational and clinical value of this report. I am sorry to say this but what the authors report is not novel and in contrast it is quite common. We know that polyglycolic acid (PGA) is a material that often can cause granulomas and we see it often occurring with PGA sutures. Similar occurrences post thoracic surgery have been reported in the literature: Mustafa Yüksel, Asli Gül Akgül, Serdar Evman, Hasan Fevzi Batirel, Suture and stapler granulomas: a word of caution, European Journal of Cardio-Thoracic Surgery, Volume 31, Issue 3, March 2007, Pages 563-565, https://doi.org/10.1016/j.ejcts.2006.11.056. Maybe, it is not as common/has not been reported with PGA sheets but the technique described by the authors (covering the resected surface and also applying fibrin glue) can be considered predisposing to granuloma development.

Response: We wish to thank the reviewer for this comment. PGA sheets may be considered predisposing to granuloma development as you mention, but we have not experienced suture granuloma by PGA suture. Suture granuloma has been well reported and usually made by non-absorbable suture such as silk. We cited the literature of Yüksel as reference No.6, but their report did
not include suture granuloma by PGA as well. In fact, foreign body reaction to PGA has been first reported by Munteau et al. in 2017 (Munteanu RM, Eva L, Dobrovăţ BI, Iordache AC, Pendefunda L, Dumitrescu N, Mihâilă D, Gavrilescu CM, Şapte E, Poeată I. Longer survival of a patient with glioblastoma resected with 5-aminolevulinic acid (5-ALA)-guided surgery and foreign body reaction to polyglycolic acid (PGA) suture. Rom J Morphol Embryol. 2017;58(2):671-680.). To make this point clearer, we have added the reference and the following to the Discussion (P8, lines 45-47): Although Munteanu et al. first reported suture granuloma by PGA suture,

Therefore, I am reluctant to recommend acceptance of this work as I am unsure of its educational and teaching value! Reviewing the included scan images and from the presented history I feel most surgeons would come to the same conclusion the authors did and would go ahead with a second resection in these patients. Maybe, in the first case a CT-guided FNB could have been performed, but that is not true for the second case. If it was, I am sure it would have saved the authors a lot of grief and fretful moments!

Response: We think that the most important point of this paper is that mass has formed in the vicinity of the surgical margin after lung resection with the elevation of the serum tumor marker level (CEA). From these two points, we thought that these cases were recurrences and chose to perform re-resection. On the other hand, it is widely known that completion lobectomy, especially after pulmonary segmentectomy, is a very difficult and dangerous procedure because of post-operative changes such as adhesion around the hilar area. In other words, we wrote this paper because we thought that the benefit would be great for both patients and surgeons if we could avoid such difficult operations.

However, we have to estimate the possibility of granuloma before resection. We would like to inform this problem widely by this manuscript, because local recurrence frequently occurs on segmental plane after pulmonary segmentectomy.

Thank you for giving me the opportunity to review this work and good luck to the authors.

Reviewer #3: Okazaki and colleagues present two interesting cases of patients undergoing re-operative resection for FDG positive lesions following lung cancer resection. In both cases, the hyper metabolic lesions were negative for malignancy and showed granulomatous lesions possibly associated with The PGA staple reinforcement sheets used during the initial lung resection. I hope the authors could further improve the manuscript by addressing the following comments/questions:

- The formation of granulomas in response to PGA sheet is very interesting. Cam you elaborate on the proximity of the granulomatous lesions with the staple line and PGA sheets on imaging and intraoperatively? Was there a pathological correlate to PGA sheets on the re-resection specimen? Also, were infectious etiologies of granulomas exuded?

Response: Unfortunately, we were not able to find out where PGA sheets were. We think it is difficult, because PGA degrades within a month and cannot be seen in the specimen. As there was no evidence of infection such as mycobacteria and fungus, we added the following to the manuscript (P7, lines 54-56. P8, line 29): There was no evidence of infection such as mycobacteria and fungus.

- Please explain the decisions to pursue or not pursue tissue conformation of recurrence prior to re-resection, given the morbidity of at least one of the described cases.
Response: In accordance with the reviewer's comment, we added “The pathological diagnosis of the nodule with bronchoscopic or CT guided biopsy was difficult because of the location. However, these clinical findings suggested highly suspected local recurrence of lung cancer.” in Case 1 (P7, lines 40-44).

- It would be immensely interesting for the reader to know the denominator of true positive and false-negative disease following re-operative lung resection following resection of early stage lung cancer. Can you provide this data from your institution?

Response: We wish to thank the reviewer for this comment. I agree with this point, and we added the following to the manuscript (P9, line 11): In our institution, there were six reoperations against suspected recurrence tumor between 2011 and 2017, and two of them were granulomas presented in this report.