Dear editor and dear reviewers

First of all, thank you for the review of our manuscript. We sincerely appreciate all the valuable comments and suggestions that allowed us to improve the quality of the manuscript. Our responses to your comments are described below in a point-by-point manner and we have corrected the manuscript in red letters. We hope that our manuscript will be acceptable for publication.

Reviewer #1:

Specific Comments to Authors: The Authors present an interesting and rare case of septic shock due to Granulicatella adiacens after the EUS-FNB of a splenic mass. The final diagnosis was diffuse large B-cell lymphoma. Although it is a rare complication, and the guidelines don't recommend antibiotics before solid masses biopsies, they conclude that prophylactic antibiotics might be considered when a splenic mass is biopsied in patients with hematologic malignancies who have weak immunity and are vulnerable to bacterial infections. The manuscript is well written and clear. The pictures are of good quality. Just two comments: • Please, specify how many passes were performed with the FNB needle. • Did the Authors used contrast medium during the examination?

➔ Thank you for the comment. Three needle passes were performed with the FNB needle and we did not use contrast medium during the examination. We have added this in the "further diagnostic work-up" section (page 6, line 16 and line 18).

Had they the impression that the mass was necrotic inside or had some ultrasound appearances that might have represented a risk factor for infection?

➔ There was no necrotic change of the splenic mass and we could not find any risk factor for infection during the endoscopic ultrasound (EUS) examination. We have added this in the "further diagsnotic work-up" section (page 6, line 18).

Reviewer #2:

Specific Comments to Authors: The authors reported a case of splenic lymphoma who developed septic shock after EUS-FNB. It is a good case to discuss the indication of EUS-FNB for splenic lesions and the use of antibiotics during the procedure. However, I have some concerns in this case report which need to be addressed.

Major 1. As the authors mention in the main document, the most common primary malignant tumor of the spleen is lymphoma. However, the authors initially suspected a rare tumor such as a sclerosing angiomatoid nodular transformation. What was the reason to suspect a rare tumor more than a lymphoma in this case? Have you performed blood exams such as sIL-2R, immunoglobulin, and complement which may show abnormalities in lymphoma? Please clarify this point.

- ➔ Thank you for the comment. We suspected sclerosing angiomatoid nodular transformation (SANT) of the spleen first because of the following reasons: i) the lesion was found incidentally and the patient had no B symptoms (fever, night sweat, or body weight loss); ii) there was no other organ involvement or perihilar lymphadenopathies in CT or MRI; iii) MRI showed hypointense in T1 and T2 weighted images with peripheral enhancement in T1 weighted image, which were considered as MRI findings of SANT rather than lymphoma. Splenic lymphomas are usually secondary and primary splenic lymphoma is rare, although SANT is also a rare disease. However, conclusive diagnosis of the splenic lesion was impossible and we had to perform biopsy. We have added this point in the discussion section (from page 8, line 22 to page 9, line 19)
- ➔ We performed blood exams of soluble interleukin-2 receptor (sIL-2R), immunoglobulin, and complement after the EUS-guided cytopathology confirmed poorly differentiated malignancy. sIL-2R was elevated to 3891 U/mL (normal 158~623), and complement 3 was decreased to 69.1 mg/dl (normal 90~180). However, immunoglobulin E and complement 4 levels were within normal limits. We have specified this in the manuscript in the "further diagnostic

work-up" section (page 6, line 25-27).

2. Has this patient had any multiple lesions of lymphoma other than spleen? If not, does he need chemotherapy after resection of the splenic tumor? And how do you assess the treatment effect?

→ Thank you for the comment. There was no lymphomatous involvement of the other organs except for the spleen. We performed workup, treatment and follow-up according to National Comprehensive Cancer Network (NCCN) guideline. Our patient was in stage 1 with non-bulky (<7.5cm) mass and 0 of international prognostic index (IPI). In this case, 4-6 cycles of chemotherapy (Rituximab/Cyclophosphamide/Doxorubicin/Vincristine /Prednisolone: R-CHOP) with or without involved site radiotherapy have to be performed. And we assessed the treatment effect by computed tomography every 6 months. We have added this to the manuscript in the "treatment" and "outcome and follow-up" section (page 8, line 4-15).

3. I agree with the authors that since the patients with hematologic malignancies have immunological disorders, they have higher risk to cause infection after EUS-FNB. Therefore, I think it is important to perform exams to help diagnosis and determine the stage of lymphoma, such as contrast-enhanced CT, FDG-PET, and laboratory tests before EUS-FNB. Because if there are multiple lesions, sampling from other lesions can be considered. And if there is no alternative method to make diagnosis, EUS-FNB may be considered with prophylactic antibiotics. Please discuss this point in the main document.

→ Thank you for your comment. As CT and MRI showed no other mass except for the spleen, we had no choice but to perform EUS-FNB in the spleen. However, given that most splenic lymphomas are secondary, we agree that various imaging tests and laboratory tests to diagnose and stage lymphoma are needed. Also, to decrease the risk of EUS-FNB associated infection, if involvement of peripheral lymph nodes are

found, biopsy could be performed at these sites. We have discussed this point in the main document (from page11, line 22 to line 27).

4. Please describe histopathological diagnosis of EUS-FNB sample in detail not only cytopathology diagnosis.

→ Histopathology revealed mostly blood clots and few inflammatory cells and cytopathology was suspicious for poorly differentiated malignancy. We added histopathology finding in the "further diagnostic work-up" section (page 6, line 22).

Minor Page 4, line 3. Therefore, we suggests→Therefore, we suggest Page 8, line 26. it is most commonly presents→it is most commonly presented.

➔ Thank you for the comment that made the sentence to be more accurate. We have corrected these grammatical mistakes.

Reviewer #3:

Specific Comments to Authors: Thank you for reviewing an interesting case report in which septic shock might be induced by EUS-FNB of the spleen. The procedure might trigger the infection, however, it was not evident due to its incubation period. I have the following comments. Major points Association of the procedure and the infection needs to be thoroughly discussed. Based upon the clinical course that the patient developed septic shock 10 days after the EUS-FNB, we could not conclude that the procedure resulted in this infection. Normally, when does EUS-FNB related infection happen after the sampling of tissues other than solid organs? When did his fever or symptoms associated with septic shock start? Any possibilities that the splenic abscess existed prior to EUS-FNB? Basically, the description regarding the patients' clinical course would be inadequate, more detailed clinical pictures should be added.

➔ Thank you for your thoughtful comment. Limited data are available regarding the incubation period for infection after EUS-guided sampling due to the rarity of this event. In retrospective studies, patients presented symptoms to suspect

infection about 2 to 7 days after EUS-FNA of pancreatic cystic lesions, and mediastinal infection developed 2 to 15 days after EUS-FNA of mediastial lesions. Our patient felt chillness 7 days after EUS-FNB and septic shock developed after 10 days of the procedure. Initial EUS of the splenic lesion showed no necrosis or abscess formation and laboratory findings showed normal inflammatory markers (including WBC and CRP). MRI obtained on readmission showed abscess formation of the splenic lesion, which was not found in the intial MRI. Therefore, we suspect that splenic abscess and septic shock developed after the procedure. We have added discussed this point in page 10, line 20 to page 11, line 2.

Also, even though the infectious complications after EUS-FNB of solid organ are very low and diffuse large B-cell lymphoma is the most common primary splenic tumor, why do the authors think this happened to this patient? In addition to the patients' hematologic malignancy, are there any other precipitations or triggers?

→ Thank you for your comment. The risk factors of infection after EUS-guided sampling are cystic lesions, ascites or pleural fluid around the lesions, and necrosis. However our patient did not have these risk factors. Also, other than the hematologic malignancy, he had no other risk factors for infection such as diabetes mellitus. Therefore, we think that splenic infection was likely from his immunocompromised status (lymphoma). We have discussed this point in page 10, line 3-12.

Minor points 1. Please specify whether the MRI image was with or without contrast. Was contrast-enhanced MRI was examined initially or later? Generally, dynamic MRI would help us determine the lesions more precisely.

➔ We agree with your opinion. We examined MRI images with contrast initially and later. We have described the MRI findings in more detail in "imaging examinations" and "clinical course" section (page 6, line 6-12and page 7, line 8-14). Also, we have added the MRI findings of splenic lymphoma and SANT in the "discussion" section (from page 8, line 22 to page 9, line 12 ).

2. How many times of the EUS-FNB were attempted?

→ Three needle passes were performed during the EUS-FNB. We have added this in the "further diagnostic work-up" section (page 6, line 18).

3. From the bacteriological standpoint, please consider describing the method to definitely identify the G. adiacens.

→ We cultivated bacteria of blood in a liquid medium for a couple of days and it was identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). We have added this method in the "clinical course" section (page 7, line 17).

4. When was splenectomy performed?

→ Intravenous antibiotics were administered for 12 days and the patient was discharged. After recovery from the infection, he got vaccination to reduce the risk of infections with encapsulated organisms after splenectomy. Splenectomy was performed 4 weeks after vaccination, 40days after septic shock developed. We have added this in the "final diagnosis and treatment" section (page 8, line 1-2).

5. Please consider including the discussion of which antibiotics are recommended.

→ There is no prospective randomized study in which antibiotics should be administered before the EUS-guided sampling. In most studies, beta-latam antibiotics or fluoroquinolones intravenously at first followed by orally for 3~5 days were used. Therefore, this preventive method could be used for EUS-FNB of a splenic mass. We have discussed this point from page 11, line 28 to page 12, line 13.