Peer Review File

Article information: https://dx.doi.org/10.21037/apm-21-1148

Reviewer A

The authors reported a case of pseudoprogression in a UC patient with Lynch syndrome treated with atezolizumab.
This is a well written and interesting report.

Major point
What is the rationale for continuing treatment? What is the standard of care for pleuritis?
Did you use steroids or immunosuppressive drugs? If not, please explain why you did not use them.

Minor point
Fig.4 is difficult to read. Please make the numbers larger.
This report is considered to be a case of pseudoprogression with atezolizumab.
I would like to know what the implications of Lynch syndrome were in this case.
Please describe the relationship between Lynch syndrome and pseudoprogression, if you know.

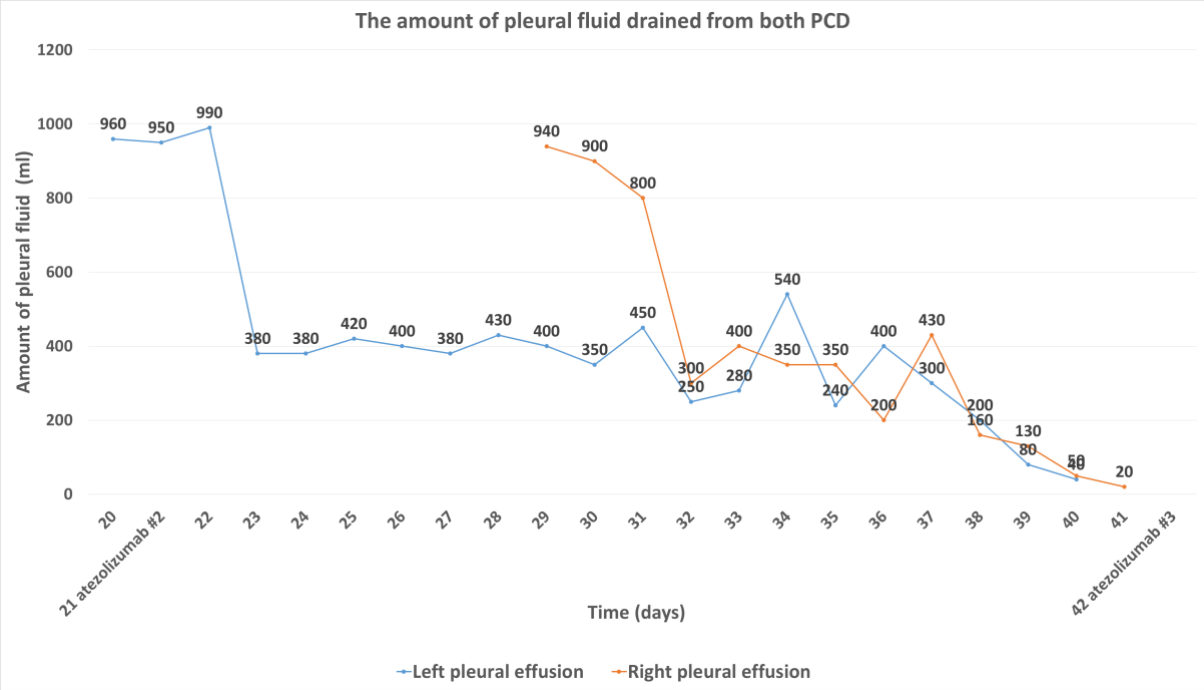
Major point
Comment 1: What is the rationale for continuing treatment?
Reply 1: There are research results that show a good response to immune checkpoint inhibitor in Lynch syndrome, and the patient's symptom do not worsen, so the possibility of pseudoprogression was considered and treatment was maintained.
Changes in the text: Page 11, lines 19-22 : There are no clinical studies on the efficacy of ICIs in LS-associated UC, but some case reports have shown them to be effective (3, 16, 17). This patient was expected to respond to atezolizumab treatment as he had ureteral cancer with LS and as his symptoms did not worsen, ICI therapy was maintained.

Comment 2: What is the standard of care for pleuritis?

Reply 2: Treatment for pleuritis depends primarily on the underlying cause. In this patient, pleural fluid drainage was initially performed considering the occurrence of pleural effusion due to cancer progression. If the immune-related adverse event is considered, additional steroids or immunosuppressive drugs can be used.
Changes in the text: Page 10, lines 9-11 : Our patient showed spontaneous resolution of pleural effusion by only pleural fluid drainage with PCD without steroids or immunosuppressive drugs at 7 weeks after atezolizumab, similar to the pseudoprogression cases.

Comment 3: Did you use steroids or immunosuppressive drugs? If not, please explain why you did not use them.
Reply 3: Steroids or immunosuppressive drugs were not used. Since rib metastasis increases together, the possibility of disease progression or pseudoprogression was considered greater than immune related adverse events. In addition, since there was no worsening of the patient's symptoms after pleural fluid drainage, additional treatment with steroids or immunosuppressive drugs was not considered.
Changes in the text: Page 10, lines 9-11 : Our patient showed spontaneous resolution of pleural effusion by only pleural fluid drainage with PCD without steroids or immunosuppressive drugs at 7 weeks after atezolizumab, similar to the pseudoprogression cases.

Minor point
Comment 1: Fig.4 is difficult to read. Please make the numbers larger.
Reply 1: The numbers have been corrected to be larger and darker.
Changes in the text:



Comment 2: This report is considered to be a case of pseudoprogression with atezolizumab. I would like to know what the implications of Lynch syndrome were in this case.

Please describe the relationship between Lynch syndrome and pseudoprogression, if you know.

Reply 2: GERCOR NIPICOL phase II study analyzed the effects of nivolumab plus ipilimumab in 57 patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer, and was associated with Lynch syndrome in 36 patients (56%). A total of 2 pseudoprogression patients (3.5%) occurred. One patient was occurred at week 6 in a 68-year old man from a MLH1/PMS2-negative, and the other patient was occurred at week 36 in a 47-year old woman with a MSH2/MSH6-negative. In conclusion, pseudoprogression is rare in patients with MSI/dMMR metastatic colorectal cancer treated with nivolumab and ipilimumab.

Changes in the text: Page 11, lines 14-18 : Only two patients showed pseudoprogression (3.5%) in the above study. The first occurred at week 6 in a 68-year old man who was MLH1/PMS2-negative, and the other occurred at week 36 in a 47-year old woman who was MSH2/MSH6-negative. In conclusion, this study showed that the incidence of pseudoprogression in MSI/dMMR may be rare.

Reviewer B

The authors describe an interesting case report on a highly relevant topic. The conclusion that

pseudoprogression needs to be considered when using ICI seems reasonable. However, both in the case description and in the discussion, there are considerable linguistic and content-related deficiencies that need to be remedied before a possible publication.

Major points:
The entire work needs to be linguistically revised. There are frequent word repetitions (for example: page 3 lines 9-10 and lines 25-31; page 7 lines 14&17) and grammatical inconsistencies.

Some passages are clearly too verbose. They should be shortened and reduced to the essentials (for example: page 3 lines 19-21; page 4 lines 14-16; page 5 lines 3-11; page 6 lines 6-14).

The key message of the paper needs to be clarified in the discussion. The phenomenon of pseudoprogression could be further elucidated (e.g. with regard to potential immunological mechanisms). In contrast, the detailed explanations of LS at this point do not seem to be purposeful.

Minor point:
Atezolizumab therapy (page 4 line 10) should be referred to as immunotherapy rather than chemotherapy.

Major points:
Comment 1: The entire work needs to be linguistically revised. There are frequent word repetitions (for example: page 3 lines 9-10 and lines 25-31; page 7 lines 14&17) and grammatical inconsistencies.
Reply 1: English editing was performed again for the entire contents by professional editors at Editage.
We have modified our text as advised. (contents before revision – changes in the text : contents after revision)
① Page 3 lines 9-10 (7-12) : This patient was diagnosed with urothelial carcinoma originating from the left ureter with LS and showed progression of multiple rib metastases during atezolizumab treatment. During this period, a large pleural effusion occurred bilaterally. As the rib metastasis improved while maintaining the atezolizumab treatment, the bilateral pleural

effusion also improved. We present a rare case of transient bilateral pleural effusion with pseudoprogression of multiple rib metastases that developed after treatment of urothelial carcinoma with atezolizumab in LS.

Changes in the text: Page 4 lines 18-20 : We present a rare case of transient bilateral pleural effusion with pseudoprogression of multiple rib metastases that developed after treatment of urothelial carcinoma from the left ureter with atezolizumab in LS.

② Page 3 lines 25-31 : Abdominal computed tomography (CT) at admission revealed a 2.8-cm tumor in the left ureter, which resulted in left hydronephrosis. ^{18}Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/CT (^{18}F-FDG PET-CT) revealed FDG uptake in the left ureter, adrenal metastasis, and multiple bone metastases in the skull, ribs, spine, left scapula, manubrium, pelvic bones, and right femur. Whole-spine magnetic resonance imaging revealed a compression fracture due to metastasis in the lumbar spine (L5), and multiple spinal metastases were identified.

Changes in the text: Page 5 lines 10-13 : Abdominal computed tomography (CT) at admission revealed a 2.8-cm tumor in the left ureter. ^{18}Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/CT (^{18}F-FDG PET-CT) revealed FDG uptake in the left ureter and adrenal gland, and multiple bone metastases in the skull, ribs, spine, and pelvic bones.

③ Page 7 lines 14&17 (13-18) : There are no clinical studies on the effectiveness of ICIs in LS-associated UC, but some case reports mention that they show good effects (3, 15, 16). This patient showed pseudoprogression of bone lesions after atezolizumab treatment, but after the third cycle, the lesions improved, and a good response to continued ICI therapy is expected in the future. This patient was expected to respond to atezolizumab treatment as he had ureteral cancer with LS; therefore, ICI therapy was maintained even with the increase in size of the bone lesions and pleural effusion.

Changes in the text: Page 11 lines 19-22 : There are no clinical studies on the efficacy of ICIs in LS-associated UC, but some case reports have shown them to be effective (3, 16, 17). This patient was expected to respond to atezolizumab treatment as he had ureteral cancer with LS and as his symptoms did not worsen, ICI therapy was maintained.

Comment 2: Some passages are clearly too verbose. They should be shortened and reduced to the essentials (for example: page 3 lines 19-21; page 4 lines 14-16; page 5 lines 3-11; page 6 lines 6-14).

Reply 2: We have modified our text as advised. (contents before revision – changes in the text : contents after revision)

① Page 3 lines 18-21: Nine years ago, he was diagnosed with early gastric cancer and ascending colon cancer. He underwent laparoscopy-assisted distal gastrectomy, Billroth-1, and hemicolectomy. The gastric cancer was diagnosed as adenocarcinoma with a tumor size of 0.9×0.7 cm, T1aNO, and the ascending colon cancer was a well-differentiated adenocarcinoma, 2.1×1.9 cm in size, T1N0.

Changes in the text: Page 5 lines 4-6 : Nine years ago, he was diagnosed with early gastric and ascending colon cancer simultaneously. He underwent laparoscopy-assisted distal gastrectomy, Billroth-1, and hemicolectomy, and stages of each cancer were T1aN0 and T1N0, respectively.

② Page 4 lines 13-16 : Eleven days after atezolizumab administration, it was suspected that the patient had pleural effusion due to the general haziness of the left lung on a chest radiograph (*Figure 2*). We attempted to obtain a left lateral decubitus view of the chest; however, because of pain, the patient was unable to lie laterally. High-resolution computed tomography (HRCT) was used to enable differentiation from other lung lesions; thus, moderate to large amounts of left pleural effusion were confirmed, and an increased size of the left rib mass was observed (*Figure 3*).

Changes in the text: Page 6 lines 7-10 : Eleven days after atezolizumab administration, the patient was suspected to have pleural effusion due to the general haziness of the left lung observed on a chest radiograph (*Figure 2*). High-resolution computed tomography (HRCT) revealed moderate to large amounts of left pleural effusion and an increased size of the left rib mass (*Figure 3*).

③ page 5 lines 3-11 : Twenty-seven days after the first cycle of atezolizumab (6 days after the second cycle), chest X-rays revealed haziness across the right lung (*Figure 2*), and again decubitus imaging could not be obtained due to pain. HRCT revealed a large right pleural effusion, and increased size of the right and left rib masses was observed (*Figure 3*). On the following day, right chest PCD was performed; approximately 1000 mL was drained over 3 days and then 300–400 mL/day (*Figure 4*). Pleural fluid analysis found the following: protein, 2.2 g/dL (total serum protein: 5.0 g/dL); LDH, 607 IU/L (serum LDH: 1287 IU/L); white blood cell count, 510/mm^3 (72% lymphocytes); and ADA, 12.8 U/L (normal: 0–40 U/L). Right pleural effusion was also exudative and lymphocyte-dominant. Pleural fluid cytology revealed only some inflammatory cells and mesothelial cells.

Changes in the text: Page 7 lines 6-12 : Twenty-seven days after the first cycle of atezolizumab

(6 days after the second cycle), chest X-rays revealed haziness across the right lung (*Figure 2*), and HRCT revealed a large right pleural effusion, and an increased size of the right and left rib masses was observed (*Figure 3*). On the following day, right chest PCD was performed, and the amount of pleural fluid drainage was similar to that on the left. (*Figure 4*). Right pleural effusion was also exudative, lymphocyte-dominant, and cytology revealed only some inflammatory cells and mesothelial cells.

④ Page 6 lines 6-14 : We considered the possibility of irAEs and pseudoprogression as the initial causes of the pleural effusion. The patient had multiple rib metastases at diagnosis, and the size of the rib metastases increased temporarily after treatment with atezolizumab. The patient had chest wall invasion due to rib metastasis. He had more large-sized rib metastasis lesions on the left side; thus, pleural effusion was considered to have developed first on the left side 11 days after atezolizumab treatment. Right pleural effusion developed 27 days after treatment with atezolizumab. Generally, irAEs require immunosuppressive therapy, such as steroids, and they rarely improve spontaneously. We believe that the cause of both occurrences of pleural effusion were secondary responses to rib mass pseudoprogression.
Changes in the text: Page 9 lines 14-20 : We considered the possibility of irAEs and pseudoprogression as the initial causes of pleural effusion. The patient had chest wall invasion due to rib metastasis, and the size increased after treatment with atezolizumab. He had a larger rib mass on the left side; thus, pleural effusion of the left lung developed earlier, 11 days after atezolizumab treatment. The right pleural effusion developed after 27 days. In general, irAEs require immunosuppressive therapy, such as steroids. We believe that the causes of both occurrences of pleural effusion were secondary responses to rib mass pseudoprogression.

Comment 3: The key message of the paper needs to be clarified in the discussion. The phenomenon of pseudoprogression could be further elucidated (e.g. with regard to potential immunological mechanisms). In contrast, the detailed explanations of LS at this point do not seem to be purposeful.
Reply 3: ① Added more immunological mechanism of pseudoprogression.
Changes in the text: Page 10 line 12-21 : Although there have been many studies on pseudoprogression, the exact molecular mechanism has not yet been established. The major mechanism involves the infiltration of immune cells, such as CD4 T cells, CD8 T cells, and macrophages. After ICI therapy, activated immune cells infiltrate the tumor lesion to kill cancer

cells, and more inflammatory cells are induced by antigens secreted from dead cancer cells. During this process, vascular tears and hemorrhage can be induced in the tumor tissue, and edema occurs due to inflammatory reactions and hemorrhage. Necrotic byproducts are generated from dead cancer cells, and the unabsorbed portion can accumulate in the lesion. Inflammatory cell infiltration, hemorrhage, edema, and necrotic byproducts can temporarily enlarge the tumor lesion, which can be observed radiologically as a pseudoprogression (11).

② The detailed explanations of LS have been shortened.

In addition, the patient presented with LS. Urothelial carcinoma (UC) is the third most common type of cancer in LS-associated tumors (3). Urothelial carcinoma linked to LS is the most common upper urinary tract (UUT) and accounts for approximately 20% of all UC cases (3). The cumulative lifetime risk of developing UC of the UUT ranges from 3.2 to 6.0%, which is 7.6–22-fold higher risk than in the general population (11). LS-related UC is known to develop in younger patients and more commonly in female patients (12). Patients with *MSH2* variants were reported to have the highest risk of developing UC, with an odds ratio of 4.6 (p=0.001) (13). The difference was that this patient was a relatively elderly man and had mutations in *MLH1* and *MSH2*.

Changes in the text: Page 10 line 22 – Page 11 line 5 : Moreover, the patient presented with LS. Urothelial carcinoma (UC) is the third most common type of cancer in LS-associated tumors, and UC linked to LS is the most common in the upper urinary tract (UUT) (3). The cumulative lifetime risk of developing UC of the UUT is 7.6–22-fold higher than that in the general population (12). LS-related UC is known to develop more commonly in younger and female patients with *MSH2* variants (13, 14). However, this patient was a relatively elderly man with mutations in *MLH1* and *MSH2*.

Minor point:

Comment 1: Atezolizumab therapy (page 4 line 10) should be referred to as immunotherapy rather than chemotherapy.

Reply 1: We have modified our text as advised.

Changes in the text: Second-line immunotherapy (1200 mg atezolizumab) was administered at 3-week intervals. (page 6 line 4)