Peer Review File

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Reviewer Comments

Comment 1:

Neurologic symptoms, particularly in association with myocarditis, are inadequately presented. Clinically, the symptoms with bilateral ptosis appear very myasthenic, even if antibody diagnostics are negative. It can be assumed that an overlap syndrome of myasthenia and myocarditis is present, which is typical for ICI-associated side effects (see also Möhn et al. Melanoma Res. 2019;29(4):435-440.). The authors should also discuss the positive anti-SSA and ANA.

Reply 1:

Thank you for your detailed comments. Touat et al. reported that only 5% of ICI-related myositis is associated with myasthenia gravis (Touat M et al. Neurology 2018;91:e985-e994.). We organized a MDT discussion for the differential diagnosis of the symptoms with bilateral ptosis and limb weakness. The main diseases for differential diagnosis were myasthenia and myositis. All the members of MDT group, including the neurologist, thought the diagnosis of myositis was more appropriate. Evidence list below:

1. The symptoms did not have the characteristics of myasthenia, such as lightness in the morning, heaviness in the evening, and improvement after rest. The symptoms progressed rapider and more serious than myasthenia.
2. The neostigmine test was negative.
3. Creatine kinase was the main abnormal indicator throughout the disease which was unusual with myasthenia.
4. The EMG did not found neuropathy.
5. Antibodies of neuromuscular junction were negative, including AchR-Ab, AchE-Ab, Titin-Ab, RyR-Ab and MuSK-Ab. It's very likely to be positive of

myasthenia.

The diagnosis of myasthenia gravis could be ruled out based on the existing evidence.

Möhn et al. (Möhn et al. Melanoma Res. 2019;29(4):435-440.) described four cases with metastatic melanoma who developed symptoms of acute progressive weakness. The clinical presentation and the diagnostic procedures revealed inconsistent results not typical for a classical neurological disorder. The author thought it was difficult to confirm the correct diagnosis and put forward a new ICI-induced neuropathy–myositis–myasthenia-like syndrome. But all of the four cases were not similar to the case we presented. The most important different is that we did not found neurological involvement with our case. We thought the diagnosis of myositis was more appropriate.

Most of the patients in our center (more than three-fourths) were found ANA(+) after receiving immunotherapy, accompanied by some other antibodies. But it did not develop into autoimmune disease. We have not found the exact meaning of this result so far. Further research is needed.

Changes in the text: we have list all the clinical evidence to support our diagnosis (see Page 10, line 266-289). For the positive anti-SSA and ANA, we did not think it much related to the current disease.

Comment 2:

The case description is too detailed in some places (line 62-69, line 88-90) and should be shortened.

Reply 2: We make a full description with the purpose of presenting a completed medical record. But we agreed with the comments and deleted some content in order to make it more concise.

Changes in the text:

We deleted some descriptions which we thought too detailed as advised (See Page 3, Line 67-77). And modified our text in some details (See Page 4, Line 105-107).

Comment 3:

There is no "common thread" in the discussion. What do the authors want to say? How does the case description relate to this? The discussion should be structured more stringently and better incorporate the specifics of the case report.

Reply 3: We thought the dermatologic, cardiac and muscular adverse events were relatively independent to each other. So we present the case through the timeline and discussed every side effects independently. The most important specific of this case was how the lethal irAE appeared and how we treated it.

Changes in the text:

We discussed every side effects independently, including therapeutic evidence, methods and effects (see Page 7-10, line 193-289).

In the conclusion part, we figured out what we learned from the case. IrAEs can be life-threatening. It needed early recognition and treated with high-dose corticosteroids. (see Page 11, line 291-294).

Comment 4:

The entire manuscript should be revised for grammatical and linguistic deficiencies.

Reply 4: We have carefully edited the grammatical and linguistic deficiencies in the revised manuscript. Additionally, we thanked AME editing group for re-editing this manuscript.

Changes in the text: Almost every line.

Comment 5:

The chronological sequence is not clearly represented. An additional figure with a corresponding time axis would be very helpful here.

Reply 5:

The whole process developed as follows:

2020-5-21 operation

2020-6-4 discharged

2020-6-23 the first cycle of chemotherapy combined with immunotherapy

2020-7-7 dermatologic side effect (SJS/TEN)

2020-7-16 the second cycle of chemotherapy

2020-8-1 bilateral ptosis

2020-8-8 myositis and myocarditis, ICU

2020-8-25 general ward

2020-9-1 re-discharged

Changes in the text: We modified all the phrases describing the time point to make the chronological sequence clearer as advised (see Page 3-5, line 82-138). As a result, we thought a timeline graph was not so necessary for readers to understand the course of disease.

Comment 6:

-line 51: write marketed worldwide instead auf "at home and abroad"

Reply 6: we agreed with your opinion and change it to "worldwide"

Comment 7:

-lines 54/55: aren't myositis and myocarditis much more decisive and not just an accompanying phenomenon?

Reply 7: SJS/TEN appeared first, followed by myositis and myocarditis. We thought they were relatively independent to each other. Myocarditis was indeed the most lethal one. But we want to emphasize that SJS/TEN was an early warning sign of subsequent multi-organ involvement. As a result, SJS/TEN was highlighted.

Comment 8:

-line 83: SJS/TEN may be pembrolizumab-induced (as in this case) but may also occur independently of immunotherapy

Reply 8: We agreed that SJS/TEN could be induced by many drags. But in this case, its appearance time was basically the same as other literature reports which induced by immunotherapy. Pembrolizumab had the greatest possibility of becoming an

inducement compared with other drugs the patient used. The clinical diagnosis of irAE was made by MDT team. All the members, including the dermatologist, thought it was pembrolizumab-induced.

Comment 9:

-lines 122/123: Were the IVIGs given before plasmapheresis? If so, this would be of little use, as the immunoglobulins would be washed out again with the plasmapheresis. Please specify.

Reply 9: IVIGs and plasmapheresis were both effective therapy in several immune-mediated conditions as guideline recommended. The concentration peak of immunoglobulins reached 15 minutes after IVIGs injection and began to decrease after 1 week. In this case, plasmapheresis was given one week after the IVIGs, during which the IVIG has the strongest effect. So we thought application like that was reasonable.

Comment 10:

-line 127: better write: “as the dose of methylprednisolone was reduced gradually”

Reply 10: we agreed with your opinion and modified it as advised.

Comment 11:

-line 146: Incidence of all grades of irAEs or only higher grade? Please specify.

Reply 11: We reviewed the literature. It’s the incidence of all grades of irAEs but not grade III-IV ones.

Changes in the text: we added “all grades of irAEs” (see Page 7, line 181).

Comment 12:

-line 148: Pneumonia is not necessarily an irAE. Do you mean pneumonitis?

Reply 12: Yes, we mean pneumonitis.

Changes in the text: we have modified the word as advised (see Page 7, line 183).

Comment 13:

-line 152-155: This information appears incoherent at this point.

Reply 13: we agreed with your opinion and modified it.

Changes in the text: we deleted the sentence “The National Comprehensive Cancer Network (NCCN) has updated a management guideline for immunotherapy-related toxicity to standardize the diagnosis and treatment of irAEs”(see Page 7, line 189-191)".

Comment 14:

-lines 177/178: Who is he? Do you mean the group of Bastuji-Garin and colleagues?

Reply 14: Yes. We mean the group of Bastuji-Garin and colleagues.

Changes in the text: we replaced “He” by “Bastuji-Garin et al” (see Page 8, line 215).

Comment 15:

-line 190: Which other drugs? Immunotherapeutics?

Reply 15: we mean the anti-CTLA-4 therapy.

Changes in the text: we modified it as “Anti-PD-1 therapy is associated with increased morbidity of myocarditis when it is combined with anti-CTLA-4 therapy,” (see Page 8, line 229-231)".