中文題目：晚期喉部鱗狀細胞癌患者接受 PD-1 阻斷劑 Pembrolizumab 治療後的嚴重結腸炎：免疫相關不良事件中的免疫反應病例報告

英文題目：Severe colitis after PD-1 blockade with Pembrolizumab in advanced laryngeal squamous-cell carcinoma patients: immune response in immune-related adverse events: a case report

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Introduction

Through the revolution of cancer immunotherapy, a rise in the use of therapeutic agents known as Immune checkpoint inhibitors were found to have their own distinctive adverse events, which are collectively named as "immune-related adverse events"(IrAEs). IrAEs may occur at any part of the body and the onset of these IrAEs varies. Immune-related colitis is a well-known potential adverse effect of anti-CTLA-4, that causes significant morbidity and extended hospital stays. In contrast, immune-related colitis caused by anti-PD1 was relatively rare. Pembrolizumab is a humanized monoclonal anti-PD1 antibody that has been extensively investigated in numerous malignancies. The aim of this study was to report a case of severe colitis after receiving Pembrolizumab treatment.

Case presentation

A 51-year-old male with history of alcohol drinking and heavy smoking, initially presented with gradual husky voice along with lumping sensation and left neck mass enlargement without tenderness for one month. Later on patient was diagnosed of squamous-cell carcinoma(SqCC) on the left pyriform sinus with larynx invasion, cT3N2cM0 in March, 2016.

The patient undergone several cycles of concurrent chemoradiotherapy with TPF regimen(Docetaxel, Cisplatin, Fluorouracil). Due to the disease progression, operation of left neck modified radical neck dissection(MRND) and right neck level II-IV lymph node dissection were done on July, 2017. Radiotherapy and 8 times of Cetuximab were prescribed during 17.Aug.2017 to 6.Oct.2017. Endoscopic submucosal dissection(ESD) was done on 2018/4/23, followed by radiotherapy, chemotherapy with TPF regimen and Cetuximab. As a result of the poor response of the treatments above, the patient was given chemotherapy and immunotherapy treatments, with PF, Cetuximab and Pembolizumab(100mg per month).

After five cycles of treatment, the patient presented with watery diarrhea and bloody stool. The fecal examination showed no signs of infectious bacteria. Colonoscopy revealed multiple ulcer and erosion from anal to sigmoid(Fig. 1). Pathologic report of the colonoscope biopsy showed active colitis, neutrophilis, lymphoplasmacytic cells and eosinophils infiltration. Negative finding on Periodic acid-schiff stain(PAS), Grocott's methenamine silver stain(GMS) and

cytomegalovirus(CMV) immunostain. According to the history of recent Pembrolizumab injection with no evidence of cancer involvement, immune-related colitis of Pembrolizumab was suspected. Hence, Pembrolizumab was discontinued and steroid with methylprednisolone 1mg/kg/day was infused for 10 days instead. Upon the improvement of diarrhea, we tapered the dosage of steroid gradually.

2 months later, the patient suffered from bloody stool again. Colonoscope revealed pancolitis(Mayo subscore:3) (Fig. 2) and the colonoscope biopsy showed the same as the first time, with active colitis, neutrophilis, lymphoplasmacytic cells and eosinophils infiltration. Steroid infusion was given initially and were later on prescribed with oral steroid for 1 month as symptoms improved.

Figure 1

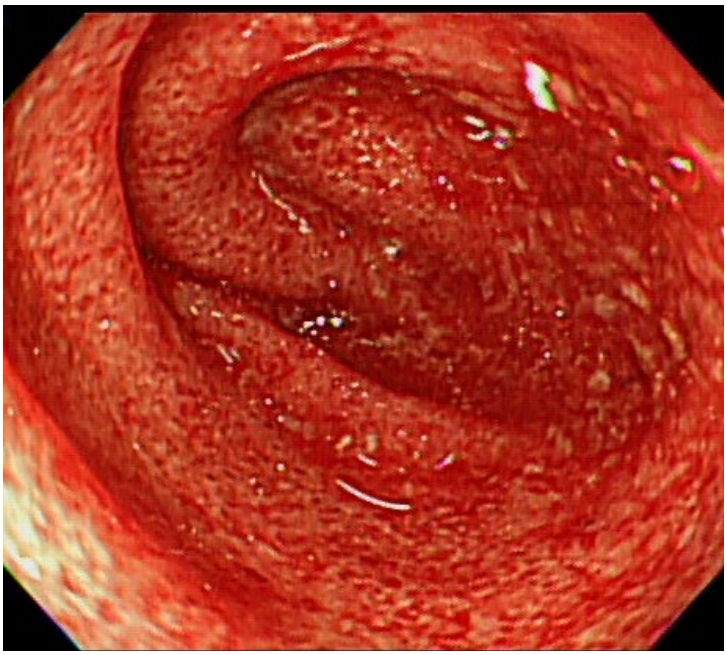

Fig. 1 - Colonoscopy revealed multiple ulcer and erosion from anal to sigmoid

Figure 2

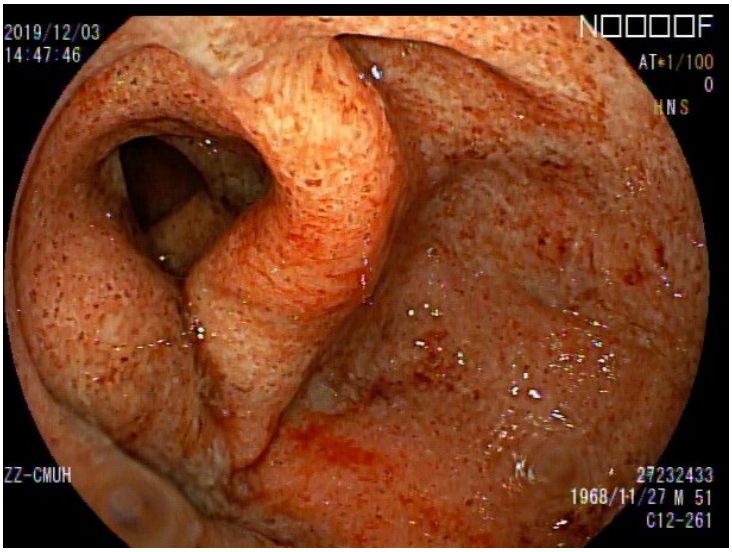

Fig. 2 - Colonoscope revealed pancolitis(Mayo subscore:3)

Discussion

Due to the uncertainty of the optimal treatment duration and dosage for Pembrolizumab, IrAEs can occur late or even after cessation of treatment. Adverse events of Pembrolizumab occurred in up to 60% of patients, but grade 3/4 toxicities were observed in <10% of cases. The frequencies of IrAEs found in clinical trials were comparable, and were mainly observed when a dosage of 10mg/kg of Pembrolizumab was prescribed. Grade 1–2 IrAEs can usually be managed symptomatically. Grade 3 and 4 IrAEs requires high dose of corticosteroids and permanent discontinuation of treatment. In this clinical case, the patient suffered from severe diarrhea, which was graded as grade 2 to 3 IrAE. The symptoms persisted even after cessation of Pembrolizumab treatment. Diarrhea was not relieved until steroid infusion was given.

Conclusion

As the arisen of the new epoch of immunotherapy treatment in cancer, many immunological complications such as IrAEs were reported and they could be clinically challenging. It was known that IrAEs can occur in any organ and they seem to be distinct, therefore the importance of clinical reports would help us gather informations of IrAEs management, provide differential diagnosis and increase the awareness of the possible complications on patients with immunotherapy treatment.

References

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