Case Report: iMDT Corner

Long-survival of a patient with esophageal cancer benefited from comprehensive treatment and MDT: a case report

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Background: Immune checkpoint inhibitors (ICIs) are emerging as important drugs for patients with locally advanced esophageal cancer (EC). Yet, immune-related adverse events (irAEs) may be a major obstacle for these population. Multidisciplinary team (MDT) is an efficient way to deal with such conditions. The aim of this study is to report a case of a stage III esophageal squamous cell carcinoma (ESCC) patient who achieved long-term survival through comprehensive treatment and MDT management, despite multiple irAEs.

Case Description: A 67-year-old man was diagnosed with stage III ESCC (cT4N1M0) in January 2021. After 2 cycles of initial immuno-chemotherapy with good efficiency, he suffered from grade 3 immune-related hepatitis (IRH) and recovered after steroid therapy. Then radical radiotherapy began as planned. However, he got pneumonia and common antibiotics and steroid showed no effect. Finally, NGS-based pathogen detection identified cytomegalovirus (CMV) infection in his sputum. Ganciclovir was prescribed to him and his condition turned better soon. During a five-month period of anti-infectious therapy and follow-up, there was no anti-tumor treatment. However, the patient's esophageal lesion was evaluated as having a partial response (PR) on computed tomography (CT) scan and cancer cells transformed to high-grade intraepithelial neoplasia through gastroscopy. He underwent endoscopic submucosal dissection (ESD) and began a five-month follow-up period. When dysplasia recurred locally, the MDT members carefully restarted ICIs since he had fully recovered from previous irAEs and we believed he benefited from long-term responses to ICIs. Despite experiencing a third irAE, that is, adrenocortical insufficiency with mild symptoms, the patient still greatly benefited from ICIs. After being diagnosed as stage III EC for about 35 months, the patient's disease was still evaluated as clinical no evidence of disease (NED).

Conclusions: EC patients with irAEs who are well managed benefited from ICIs. MDT is crucial in the management of comprehensive treatment for EC.

Keywords: Case report; esophageal cancer (EC); immune-related adverse events (irAEs); multidisciplinary team (MDT)

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Introduction

Due to the unique anatomical location of cervical esophageal cancer (EC), standard treatment typically involves simultaneous radio-chemotherapy (1,2). Research on immune checkpoint inhibitors (ICIs) and their use in combination with radio-chemotherapy as first-line therapy for inoperable locally advanced EC is ongoing (3,4). However, during ICIs treatment, immune-related adverse events (irAEs) can be problematic and significantly impact anti-tumor therapy. Since irAEs can affect nearly any organ, a multidisciplinary team (MDT) is essential for managing these complications. We report a case of a locally advanced EC patient who experienced a challenging course but ultimately achieved long-term survival and low tumor burden by full management of MDT. We present this article in accordance with the CARE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-227/rc).

Highlight box

Key findings

- Comprehensive treatment and multidisciplinary team (MDT) significantly improved the clinical outcome of an advanced esophageal cancer (EC) patient who experienced immune-related adverse events (irAEs).
- irAEs were observed and effectively managed, highlighting the importance of irAE monitoring during immune checkpoint inhibitor (ICI) therapy.

What is known and what is new?

- What is known: ICIs have shown promising efficacy in treating various cancers, including EC. However, irAEs present a significant challenge that requires careful management.
- What this manuscript adds: This case report details the successful application of MDT in anti-tumor therapy and therapy of irAEs of an advanced EC patient, leading to complete remission. It emphasizes the importance of comprehensive treatment strategies and provides insights into managing irAEs.

What is the implication, and what should change now?

- Implications and actions needed: This case highlights the potential of MDT-led comprehensive treatment approaches in improving the prognosis of patients with locally advanced EC. Similar comprehensive methods may be beneficial for other complex oncology cases. Future research should explore the broader application of this combined treatment strategy.

Case presentation

Diagnosis and initial treatment

In January 2021, a 67-year-old man with no significant medical history presented to Zhongshan Hospital of Fudan University with dysphagia. Gastroscopy revealed a protrusive lesion in the upper esophagus (18 cm from the incisor), with surface roughness and ulceration. The pathology confirmed poorly differentiated squamous cell carcinoma. The positron emission tomography/computed tomography (PET/CT) imaging showed thickening in the upper thoracic esophagus, 51 mm long, with paraesophageal lymph node metastasis, standardized uptake value (SUV)max 5.7, measuring approximately 9.7 mm in the shortest dimension. The patient was diagnosed with stage III EC (cT4N1M0). Due to lesion's upper thoracic location and length, surgery was not recommended after MDT discussion. Though the appropriate treatment for him is definitive concurrent chemoradiotherapy, considering endoscope cannot pass through due to esophageal stenosis, radiotherapy could lead to edema in the surrounding tissues, potentially causing difficulty in swallowing. Given the patient's combine positive score (CPS) of programmed death-ligand 1 (PD-L1) protein expression was 10, we chose induction immune-chemotherapy before radiotherapy after discussing with the patient. Since February 2021, the patient received 2 courses (6 weeks) of abraxane and cisplatin plus PD-1 inhibitor and CT scan showed lesion shrinkage. And the dysphagia of the patient significantly improved after treatment.

Treatment of immune-related hepatitis (IRH) and radical radiotherapy

Unfortunately, he developed grade 3 transaminitis in March 2021. General liver protecting therapy failed. After ruling out other potential causes of liver injury such as co-administered drugs, alcohol, metastatic disease, infectious hepatitis, biliary disease and autoimmune hepatitis, the members of irAEs MDT suspected IRH and recommended liver biopsy, but the patient refused. Then, empirical steroids therapy began. On April 8, he started receiving methylprednisolone (MP) at a dose of 40 mg/day. Four days later, his transaminitis improved

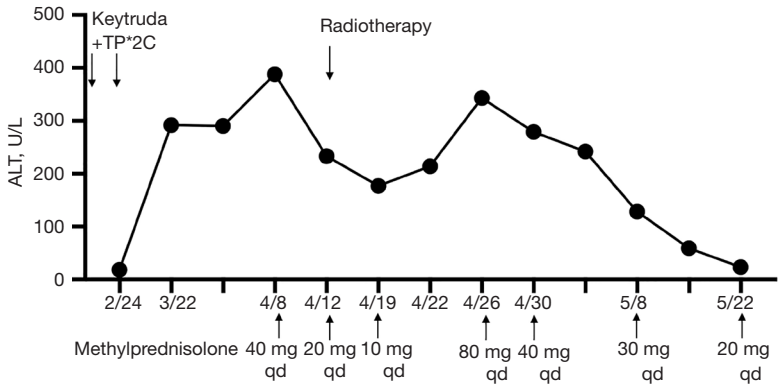

Figure 1 Process of immune-related hepatitis therapy. ALT, alanine aminotransferase; qd, quaque die; TP, abraxane plus cisplatin.

to grade 1. He then received radical radiotherapy and his MP dosage was reduced to 20 mg once daily starting on April 12. However, his transaminitis rebounded to grade 3 on April 26, prompting an increase in MP dosage to 80 mg/day and a subsequent slowly gradual reduction. His transaminitis decreased steadily and did not relapse during this period. The entire course of IRH therapy is depicted in *Figure 1*.

Treatment of pneumonitis

One issue was resolved, but another emerged. The patient was readmitted to our hospital on May 23, 2021 due to persistent dry cough, fever, and elevated inflammatory markers. Chest CT revealed pneumonia in both upper lobes and the right middle lobe. Disappointingly, after three days of treatment with levofloxacin and ceftizoxime sodium from May 23 and three days of piperacillin sodium and tazobactam sodium from May 26, no improvement was observed. As a result, sulfamethoxazole (SMZ), caspofungin, and MP 20 mg/day were administered to the patient from May 28, and doxycycline and azithromycin were added from June 2.

Timely, next-generation sequencing (NGS)-based pathogen detection revealed that the patient had been infected with human cytomegalovirus (CMV). Then ganciclovir 250 mg twice daily and immune globulin 10 g/day were immediately administered to the patient from June 3. On June 7, the patient's body temperature and inflammatory markers returned to normal, and chest CT showed that interstitial pneumonia was stable. Antibiotics were discontinued. Ganciclovir was continued until June 24, while MP was gradually reduced to 15 mg/day by August 13. By then, the treatment for pneumonitis/pneumonia was finally finished (*Figure 2*).

Long-term response to previous treatment

Despite the absence of anti-tumor treatment between March 2021 and August 2021, the esophageal lesion was evaluated as partial response (PR) in March 2021, persisting in June 2021 and August 2021 (*Figure 3*). He underwent endoscopic submucosal dissection (ESD) due to high-grade intraepithelial neoplasia in September 2021 and commenced a follow-up period of 5 months.

PD-1 antibody rechallenge

From March 2022 onwards, the patient experienced a recurrence of high-grade intraepithelial neoplasia in the upper thoracic esophagus. Given the patient's repeated local recurrences, systemic drug therapy is still necessary. However, the patient was very resistant to chemotherapy. Members of irAEs MDT examined his condition and recommended re-challenge of pembrolizumab 200 mg every 3 weeks, with close monitoring. The ICIs therapy continued until January 2023, and no evidence of disease (NED) progression was observed through regular CT evaluation.

Treatment of adrenocortical insufficiency

However, he developed severe fatigue. Laboratory test showed extremely decreased adrenocorticotropic hormone (ACTH) and cortisol. He was diagnosed as adrenocortical insufficiency. After being treated with hydrocortisone, his

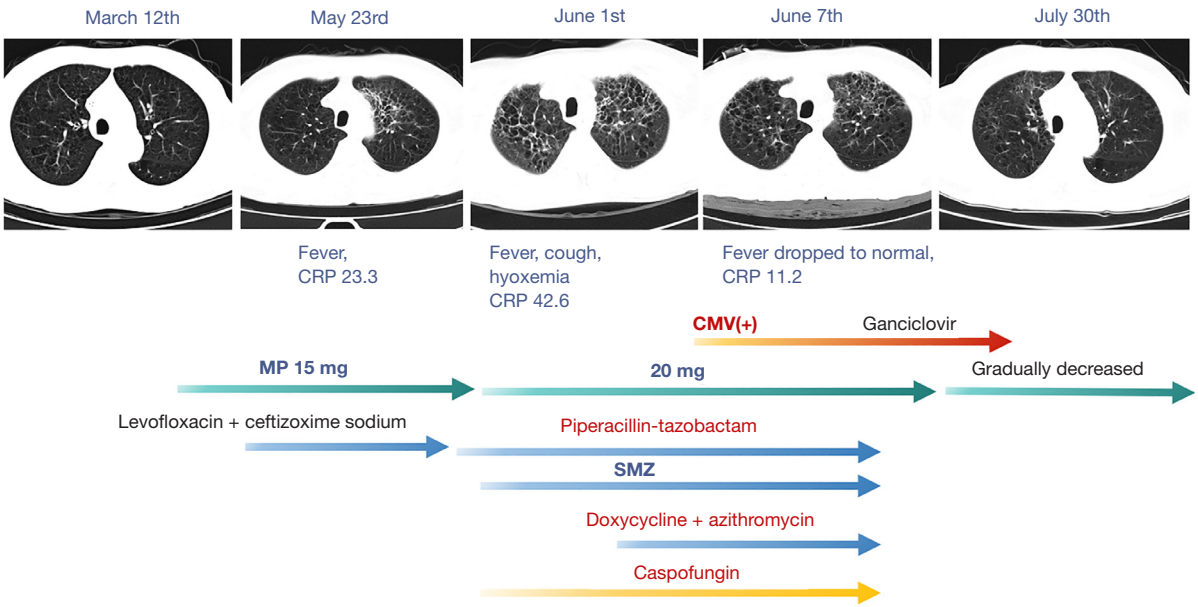

Figure 2 The entire course of treatment of pneumonitis. CRP, C-reactive protein; CMV, human cytomegalovirus; SMZ, sulfamethoxazole.

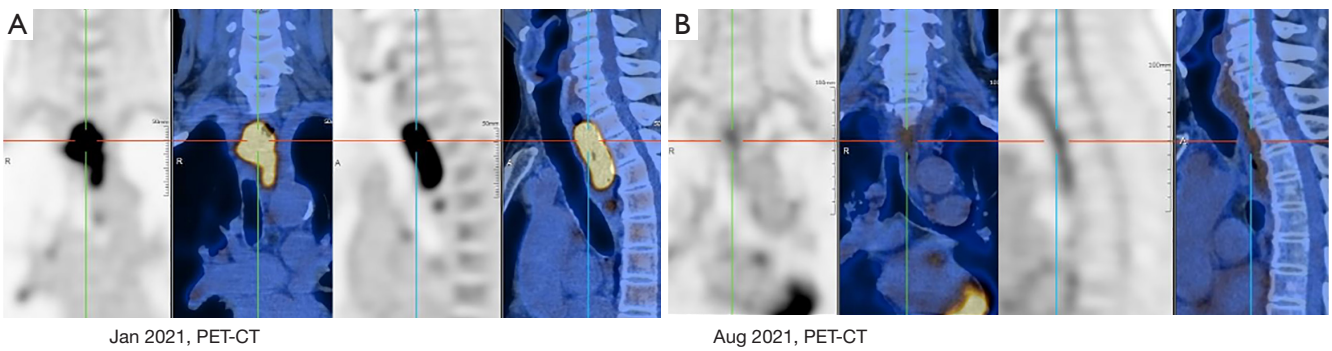

Figure 3 PET-CT imaging of the course of disease. (A) The patient was initially diagnosed with upper thoracic esophageal thickening (SUVmax 20.0), measuring 51 mm in length. Evidence of paraesophageal lymph node metastasis was observed, with an SUVmax of 5.7 and a shortest dimension of approximately 9.7 mm. (B) After 7 months of initial treatment, notable reduction in the thickness of the esophagus and a decrease in SUVmax were observed. The patient's response to treatment was deemed partial according to the RECIST. PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value; mm, millimeter; RECIST, Response Evaluation Criteria in Solid Tumors.

fatigue symptom quickly alleviated. PD-1 antibody dosing interval was hence adjusted to every 6 weeks (q6w) since then and regular CT scans showed NED progression. In October 2023, the patient received ESD again due to esophageal high-grade intraepithelial neoplasia.

The entire course is shown in *Figure 4*. After being diagnosed as stage III EC for approximately 35 months, the patient's disease was still being evaluated as clinical NED.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

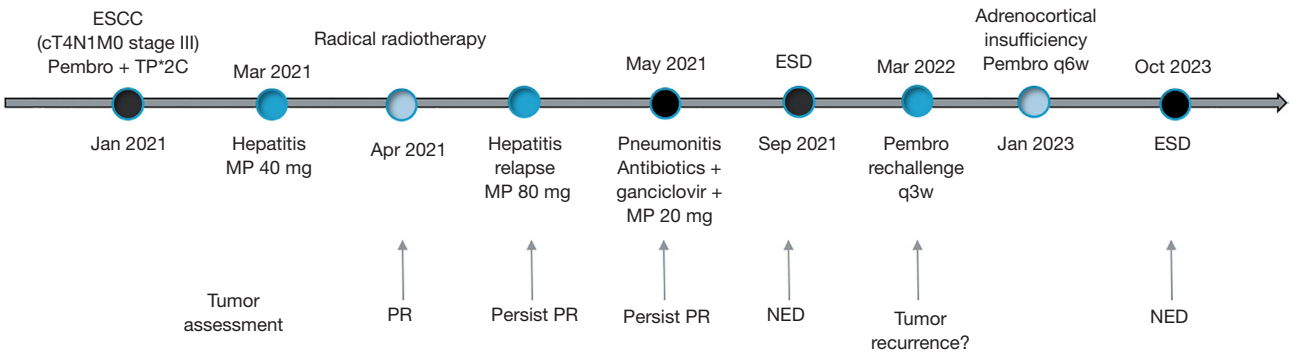

Figure 4 Whole treatment process of the patient from being diagnosed. ESCC, esophageal squamous cell carcinoma; TP, abraxane plus cisplatin; MP, methylprednisolone; ESD, endoscopic submucosal dissection; PR, partial response; NED, no evidence of disease; q6w, every 6 weeks; q3w, every 3 weeks.

International multidisciplinary team (iMDT) discussion

From January 2021 to October 2023, the patient underwent a long and arduous journey of immune-chemotherapy, radiotherapy, repeated ESD, various types of irAEs, and rechallenge with ICIs. It is clear that MDT plays a crucial role in the overall case management. The patient's prolonged survival and low tumor burden were attributed to the comprehensive MDT system at Zhongshan Hospital, which included EC MDT, irAEs MDT, early digestive tract tumors MDT, and more.

Q1: When would it be appropriate to rechallenge immunotherapy after irAEs?

Expert opinion: Dr. Yaxing Shen and Dr. Tianshu Liu

As the immune response expands, some cytotoxic T cells undergo differentiation into mature memory T cells. These memory T cells can provide long-lasting immune protection even in the absence of antigenic stimulation (5). Therefore, for patients who have experienced severe irAEs with low tumor burden, it may be appropriate to consider discontinuing medication and closely monitoring their condition. If rechallenging with ICIs is necessary for these patients, it is crucial to communicate the associated risks with them and closely monitor their progress.

According to National Comprehensive Cancer Network (NCCN) guideline, ICIs rechallenge could be considered when G2 irAEs recovered to ≤ G1. ICIs rechallenge after ≥ G3 irAEs should be conducted with caution (6).

Intervals between initial ICIs and ICIs rechallenge should be appropriate. If ICIs rechallenge was too early, toxicity might accumulate; if too late, anti-tumor therapy might be delayed. In a retrospective study, Fujisawa *et al.* found that patients with longer intervals had a significantly reduced incidence of ≥3 types of irAEs (3% *vs.* 25%, P=0.013) (7). But if PD-1 antibody is reused too late, and the immune response from the initial treatment is diminished, tumor cells may resume their dormant state. Rebuilding it might take more substantial effort. Therefore, researchers recommend rechallenging PD-1 antibody within 3 months (8).

Q2: How long should the corticosteroids therapy last? When is the appropriate time to stop it?

Expert opinion: Dr. Luoyan Ai and Dr. Yin Jun

Corticosteroid is the cornerstone for treatment of irAEs. The recommended initial dosage of corticosteroids in various guidelines is similar, but the duration and tapering principles for reducing corticosteroids are unclear. In most cases, IRH will recover within 5–9 weeks (9), or alternative explanations should be considered. Therefore, it is advisable to gradually decrease the corticosteroid dosage over a period of 5–9 weeks while closely monitoring the patient's condition. However, there is currently no established standard for treatment duration. As to immune-related pneumonitis, prednisone is recommended to taper over 4–6 weeks, or longer time for ≥ grade 3. In one prospective study, 6-week prednisone therapy demonstrated sufficient efficacy with an immune-related pneumonitis improvement rate of >90% (10).

In clinical practice, the treatment of irAEs depends on physicians' choice, and thus, the dose and duration of

corticosteroids vary widely among patients. A common problem is that physicians tend to use high dose and long period of corticosteroids because of worries about irAEs relapse. However, proper use of corticosteroids is closely related to life quality and subsequent anti-tumor therapy of patients.

Q3*: *When the cancer has transformed into a precancerous-like lesion after treatment, whether surgery or ESD should be performed or just drugs like ICIs continued?

Expert opinion: Dr. Tianshu Liu and Dr. Lijie Tan

After comprehensive treatment, the cancerous lesions of the patient turn into a precancerous-like lesion, which is common in clinical practice. But how to deal with this condition is not recorded in any guidelines. Perhaps we should make decisions based on different conditions. For patient in this case report, he suffered a lot from irAEs and his precancerous-like lesion is small, hence ESD may be an appropriate method for him to reach clinical complete response (cCR), with minimum cost. His dysplasia recurred after 6 months of cCR status. At that time, he had already recovered from all irAEs and we concluded that he benefited from ICIs, hence we tried to rechallenge PD-1 antibody with close monitoring. Here comes another question. How long can ICIs last if immunotherapy is efficient? The maintenance of ICIs in big phase-3 studies (11-13) is usually no more than 2 years. But based on our experiences, longer maintenance could be possible if clinicians estimated that the patient may still benefit from ICIs.

Conclusions

For patients with unresectable EC, we should consider various treatment options at different stages, including immunotherapies. However, the immune system can be activated by immunotherapy, causing harm to normal tissues and organs in the body, resulting in a range of irAEs. Some irAEs can be life-threatening, requiring a comprehensive MDT approach for prompt treatment and prevention of further deterioration. While addressing irAEs, the evaluation of cancer and anti-cancer therapy should not be overlooked. Only by balancing the management of irAEs and cancer can we improve patient outcomes.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-227/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-227/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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